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INTERNATIONAL APPLICATION PUBLISHED UNDER TH WO 9606097A1

(51) International Patent Classification 6 :
C07D 471/04, 471/10, 471/14, 471/20, 471/22, 487/04, 487/10, 487/14, 487/20, 487/22, 491/04, 491/044, 491/10, 491/107, 491/14, 491/147, 491/153, 491/20, 491/22, 495/04, 495/10, 495/14, 495/20, 495/22, 497/04, 497/10, 497/14, 497/20, 497/22

A1

(11) International Publication Number: WO 96/06097

(43) International Publication Date: 29 February 1996 (29.02.96)

(21) International Application Number: PCT/US95/10559

(22) International Filing Date: 18 August 1995 (18.08.95)

(30) Priority Data:
08/292,598 18 August 1994 (18.08.94) US
08/479,694 7 June 1995 (07.06.95) US

(71) Applicant *(for all designated States except US)*: ARIAD GENE THERAPEUTICS, INC. [US/US]; 26 Landsdowne Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HOLT, Dennis, A. [US/US]; 7 Brookmill Road, Stow, MA 01775 (US). SCHREIBER, Stuart [US/US]; 12 Oxford Street, Cambridge, MA 02138 (US). KEENAN, Terence [US/US]; Apartment 1L, 62 Spring Street, Cambridge, MA 02141 (US). GUO, Tao [CN/US]; 41 Belmont Street, Somerville, MA 02143 (US). LABORDE, Edgardo [UY/US]; Apartment 302A, 145 Pleasant Street, Marlboro, MA 01752 (US).

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

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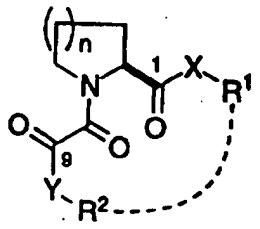
(54) Title: NEW MULTIMERIZING AGENTS

(57) Abstract

New compounds are disclosed for multimerizing immunophilins and proteins containing immunophilin or immunophilin-related domains. The compounds are of the formula: M^1-L-M^2 where M^1 and M^2 are independently moieties of formula (II), in which R^1, R^2, n, X and Y are as defined.



(II)

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New Multimerizing Agents

Background of the Invention

Aspects of the design, production and use of biological switches based on ligand-mediated multimerization of immunophilin-based recombinant proteins are disclosed in Spencer et al, 12 Nov 1993, Science 262:1019-1024 and in International Patent Applications PCT/US94/01660 and PCT/US94/08008, the full contents of each of which are incorporated herein by reference. One class of multimerizing agents is based on dimers of the macrocyclic natural product, FK506, covalently attached to each other via a synthetic linker moiety. The resultant dimers ("FK1012" molecules) are characterized by high binding affinities for immunophilin molecules. However, they are large, complex molecules which can be inconvenient to produce. New methods and materials for multimerizing chimeric proteins containing immunophilin moieties would be desirable, where the methods and materials involve smaller, simpler multimerizing agents which retain a high binding affinity for their coordinate immunophilins, but which are more convenient to produce and are more readily amenable to structural modification.

Description of the Invention

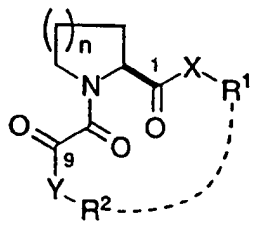
This invention provides a new method and materials for multimerizing immunophilins (including naturally occurring immunophilin proteins as well as chimeric proteins containing immunophilin-derived domains) based on N-oxalyl-pipecolyl and N-oxalyl-prolyl ligand moieties. ("Multimerization" as the term is used herein encompasses dimerization and higher order multimerization.)

The invention relates to immunophilin multimerizing agents of formula I,

$$M^1\text{-}L\text{-}M^2$$

(I)

and pharmaceutically acceptable salts thereof, where M^1 and M^2 are independently moieties of formula II:



(II)

where n = 1 or 2;

X = O, NH or CH_2;

Y = O, NH, NR^3, or represents a direct, i.e. covalent, bond from R^2 to atom 9;

R^1, R^2, and R^3 are independently C_1-C_{20} alkyl or aryl;

wherein alkyl is intended to include both saturated and unsaturated straight chain, branched, cyclic, or polycyclic aliphatic hydrocarbons which may contain oxygen, sulfur, or nitrogen in place of one or more carbon atoms, and which are optionally substituted with one or more functional groups selected from the group consisting of hydroxy, C_1-C_8 alkoxy, acyloxy, carbamoyl, amino, N-acylamino, ketone, halogen, cyano, carboxyl, and aryl (unless otherwise specified, the alkyl, alkoxy and acyl groups preferably contain 1-6 contiguous aliphatic carbon atoms);

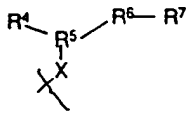
aryl is intended to include stable cyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated C_3-C_{14} moieties, exemplified but not limited to phenyl, biphenyl, naphthyl, pyridyl, furyl, thiophenyl, imidazoyl, pyrimidinyl, and oxazoyl; which may further be substituted with one to five members selected from the group consisting of hydroxy, C_1-C_8 alkoxy, C_1-C_8 branched or straight-chain alkyl, acyloxy, carbamoyl, amino, N-acylamino, nitro, halogen, trifluoromethyl, cyano, and carboxyl (see e.g. Katritzky, Handbook of Heterocyclic Chemistry) ;

R^1 and R^2 may optionally be joined, i.e., covalently lined, together, forming a macrocyclic structure (as indicated by the dashed line in II); and

L is a linker moiety covalently linking monomers M^1 and M^2 through covalent bonds to either R^1 or R^2, not necessarily the same in each of M^1 and M^2.

Linker moieties (L), need not contain essential elements for binding to the immunophilin proteins, and may be selected from a very broad range of structural types. Preferred moieties include C_2-C_{20} alkyl, aryl, or dialkylaryl structures where alkyl and aryl are defined as above. Linker moieties may be conveniently joined to monomers M^1 and M^2 through functional groups such as ethers, amides, ureas, carbamates, and esters; or through alkyl-alkyl, alkyl-aryl, or aryl-aryl carbon-carbon bonds. Furthermore, linker moieties may be optimized (e.g., by modification of chain length and/or substituents) to enhance pharmacokinetic properties of the formula I multimerizing agent.

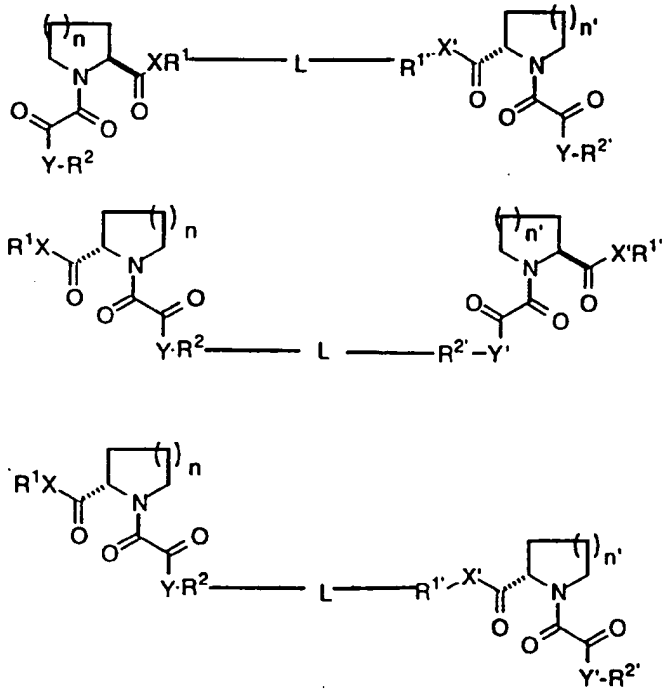
In one subset of compounds of this invention, $-YR^2$ is a straight, branched or cyclic aliphatic moiety of 1 to 8 carbon atoms, including for example ethyl, isopropyl, tert-butyl, tert-amyl, and cyclohexyl, and $-XR^1$ is a moiety of the formula



where R^4 is an aromatic or heteroaromatic group, e.g. phenyl, substituted phenyl, indolyl, pyridyl, etc.; R^5 is a straight, branched or cyclic aliphatic moiety of 2 to 8 carbon atoms, which may be optionally substituted, including ethyl, propyl, butyl, pentyl moieties and the

like; R^6 is an aromatic or heteroaromatic moiety bearing a reactive functional group, R^7, permitting covalent attachment to a linker moiety. R^7 may be -COOH, -CHO, -XH or XR^8, where X is O, S or NH (which may bear an optional substituent such as an alkyl group of 1 - 8 carbon atoms) and R^8 is $-(CH_2)_z$-COOH where z is an integer from 1 through 4.

The following formulae provide three exemplary (and non-exclusive) classes of compounds of this invention:



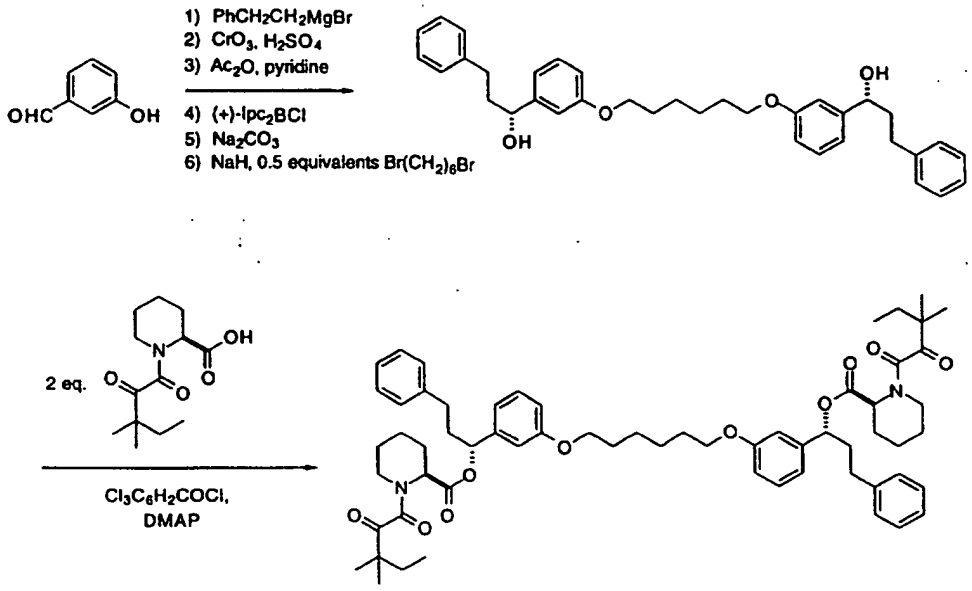
The multimerizing agents of this invention preferably cannot participate in a ternary complex with both immunophilin and calcineurin, or with immunophilin and FRAP (Brown et al., *Nature*, **1994**, *369*, 756-758) , and are therefore not immunosuppressive like FK506 or rapamycin. Additionally, it will often be preferred that the multimerizing agent be physiologically acceptable (i.e., lack undue toxicity toward the cell or organism with which it is to be used), can be taken orally by animals (i.e., is orally active in applications in whole animals, including gene therapy), and/or can cross cellular and other membranes, as necessary for a particular application.

The multimerizing agents can be used as described in PCT/US94/01617 and PCT/US94/08008, e.g. to activate the transcription of a desired gene, actuate apoptosis, or trigger other biological events in engineered cells growing in culture or in whole organisms, including in gene therapy applications. The engineered cells contain and are capable of expressing DNAs encoding proteins containing one or more immunophilin domains, such as an FKBP domain, which are capable of binding to the monomers, M (formula II), or to multimerizing agents comprising such monomers such as depicted in formulas II and in the many examples disclosed herein. In such applications, the multimerizing agent is administered to the cell culture or to the organism containing the

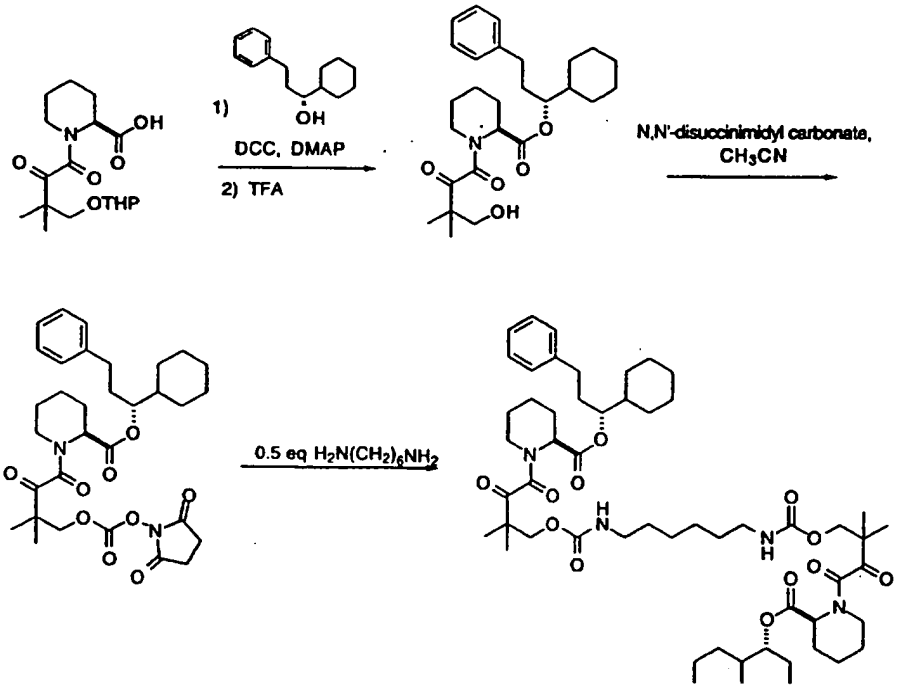
cells, as the case may be, in an amount effective to multimerize the proteins containing the corresponding ligand-binding domains (as may be observed by monitoring the transcription, apoptosis or other biological process so triggered). In the case of administration to whole organisms, the multimerizing agent may be administered in a composition containing the multimerizing agent and acceptable veterinary or pharmaceutical diluents and/or excipients. Monomers disclosed herein are also useful, both in the synthesis of dimerizing agents as disclosed in detail herein, and in their own right in view of their binding affinity for immunophilins or modified immunophilins. They may be administered to the engineered cells, or to organisms containing them (preferably in a composition as described above in the case of administration to whole animals), in an amount effective for reversing or blocking the effect of the multimerizing agent, i.e. for preventing, inhibiting or disrupting multimerization.

Compounds of this invention may be prepared by adaptation of known methods for the synthesis of N-oxalyl-pipecolyl, N-oxalyl-prolyl and related monomers. See e.g. Holt, *et al.*, *J. Amer. Chem. Soc.*,**1993**, *115*, 9925-9938; Holt, *et al.*, *Biomed. Chem. Lett.*, **1993**, *4*, 315-320; Luengo, *et al.*, *Biomed. Chem. Lett.*, **1993**, *4*, 321-324; Yamashita, *et al.*, *Biomed. Chem. Lett.*, **1993**, *4*, 325-328; Spencer et al, above; PCT/US94/01617; and PCT/US94/08008. See also EP 0 455 427 A1; EP 0 465 426 A1; US 5,023,263 and WO 92/00278.

For example, monomers may be assembled and dimerized via a number of synthetic schemes and in various orders as illustrated in the following reaction schemes.



see: Holt, *et al. J. Amer. Chem.. Soc*, **1993**, *115*, 9925-9938.


1)
DCC, DMAP
2) TFA
N,N'-disuccinimidyl carbonate,
CH3CN
0.5 eq H2N(CH2)6NH2

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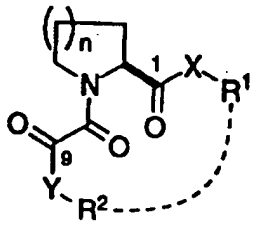

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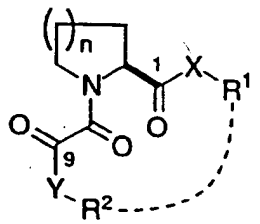
The invention relates to immunophilin multimerizing agents of formula I,

$$M^1\text{-}L\text{-}M^2$$

(I)

and pharmaceutically acceptable salts thereof, where M^1 and M^2 are independently moieties of formula II:



(II)

where n = 1 or 2;

X = O, NH or CH_2;

Y = O, NH, NR^3, or represents a direct, i.e. covalent, bond from R^2 to atom 9;

R^1, R^2, and R^3 are independently C_1-C_{20} alkyl or aryl;

wherein alkyl is intended to include both saturated and unsaturated straight chain, branched, cyclic, or polycyclic aliphatic hydrocarbons which may contain oxygen, sulfur, or nitrogen in place of one or more carbon atoms, and which are optionally substituted with one or more functional groups selected from the group consisting of hydroxy, C_1-C_8 alkoxy, acyloxy, carbamoyl, amino, N-acylamino, ketone, halogen, cyano, carboxyl, and aryl (unless otherwise specified, the alkyl, alkoxy and acyl groups preferably contain 1-6 contiguous aliphatic carbon atoms);

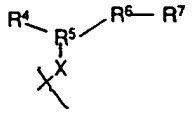
aryl is intended to include stable cyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated C_3-C_{14} moieties, exemplified but not limited to phenyl, biphenyl, naphthyl, pyridyl, furyl, thiophenyl, imidazoyl, pyrimidinyl, and oxazoyl; which may further be substituted with one to five members selected from the group consisting of hydroxy, C_1-C_8 alkoxy, C_1-C_8 branched or straight-chain alkyl, acyloxy, carbamoyl, amino, N-acylamino, nitro, halogen, trifluoromethyl, cyano, and carboxyl (see e.g. Katritzky, Handbook of Heterocyclic Chemistry) ;

R^1 and R^2 may optionally be joined, i.e., covalently lined, together, forming a macrocyclic structure (as indicated by the dashed line in II); and

L is a linker moiety covalently linking monomers M^1 and M^2 through covalent bonds to either R^1 or R^2, not necessarily the same in each of M^1 and M^2.

Linker moieties (L), need not contain essential elements for binding to the immunophilin proteins, and may be selected from a very broad range of structural types. Preferred moieties include C_2-C_{20} alkyl, aryl, or dialkylaryl structures where alkyl and aryl are defined as above. Linker moieties may be conveniently joined to monomers M^1 and M^2 through functional groups such as ethers, amides, ureas, carbamates, and esters; or through alkyl-alkyl, alkyl-aryl, or aryl-aryl carbon-carbon bonds. Furthermore, linker moieties may be optimized (e.g., by modification of chain length and/or substituents) to enhance pharmacokinetic properties of the formula I multimerizing agent.

In one subset of compounds of this invention, $-YR^2$ is a straight, branched or cyclic aliphatic moiety of 1 to 8 carbon atoms, including for example ethyl, isopropyl, tert-butyl, tert-amyl, and cyclohexyl, and $-XR^1$ is a moiety of the formula



where R^4 is an aromatic or heteroaromatic group, e.g. phenyl, substituted phenyl, indolyl, pyridyl, etc.; R^5 is a straight, branched or cyclic aliphatic moiety of 2 to 8 carbon atoms, which may be optionally substituted, including ethyl, propyl, butyl, pentyl moieties and the

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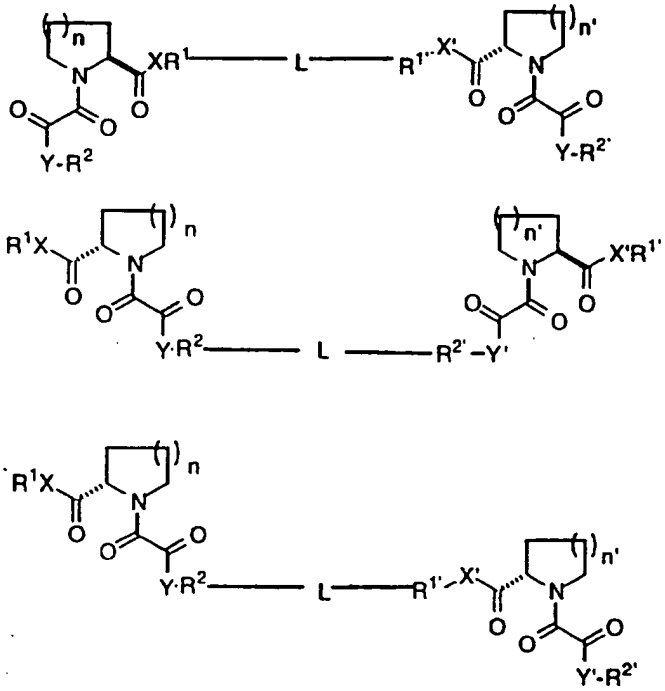
The following formulae provide three exemplary (and non-exclusive) classes of compounds of this invention:



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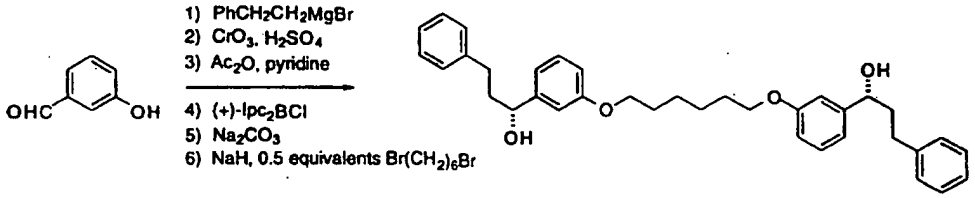
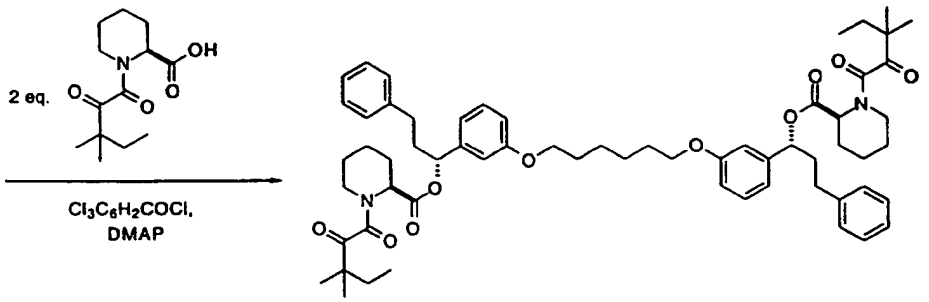
The multimerizing agents can be used as described in PCT/US94/01617 and PCT/US94/08008, e.g. to activate the transcription of a desired gene, actuate apoptosis, or trigger other biological events in engineered cells growing in culture or in whole organisms, including in gene therapy applications. The engineered cells contain and are capable of expressing DNAs encoding proteins containing one or more immunophilin domains, such as an FKBP domain, which are capable of binding to the monomers, M (formula II), or to multimerizing agents comprising such monomers such as depicted in formulas II and in the many examples disclosed herein. In such applications, the multimerizing agent is administered to the cell culture or to the organism containing the

cells, as the case may be, in an amount effective to multimerize the proteins containing the corresponding ligand-binding domains (as may be observed by monitoring the transcription, apoptosis or other biological process so triggered). In the case of administration to whole organisms, the multimerizing agent may be administered in a composition containing the multimerizing agent and acceptable veterinary or pharmaceutical diluents and/or excipients. Monomers disclosed herein are also useful, both in the synthesis of dimerizing agents as disclosed in detail herein, and in their own right in view of their binding affinity for immunophilins or modified immunophilins. They may be administered to the engineered cells, or to organisms containing them (preferably in a composition as described above in the case of administration to whole animals), in an amount effective for reversing or blocking the effect of the multimerizing agent, i.e. for preventing, inhibiting or disrupting multimerization.

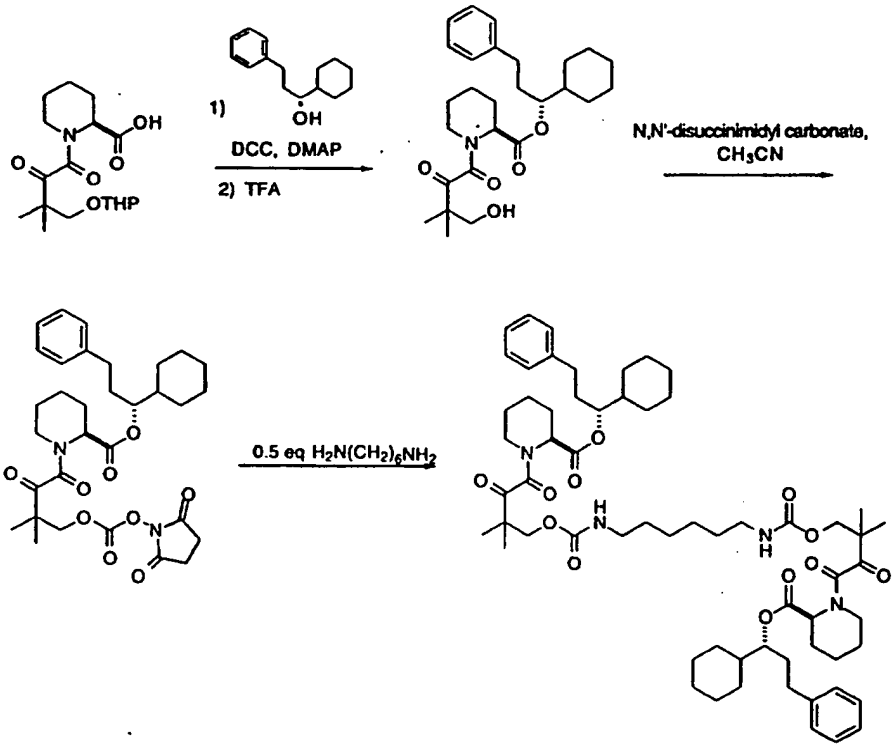
Compounds of this invention may be prepared by adaptation of known methods for the synthesis of N-oxalyl-pipecolyl, N-oxalyl-prolyl and related monomers. See e.g. Holt, *et al., J. Amer. Chem. Soc.*,**1993**, *115*, 9925-9938; Holt, *et al., Biomed. Chem. Lett.*, **1993**, *4*, 315-320; Luengo, *et al., Biomed. Chem. Lett.*, **1993**, *4*, 321-324; Yamashita, *et al., Biomed. Chem. Lett.*, **1993**, *4*, 325-328; Spencer et al, above; PCT/US94/01617; and PCT/US94/08008. See also EP 0 455 427 A1; EP 0 465 426 A1; US 5,023,263 and WO 92/00278.

For example, monomers may be assembled and dimerized via a number of synthetic schemes and in various orders as illustrated in the following reaction schemes.

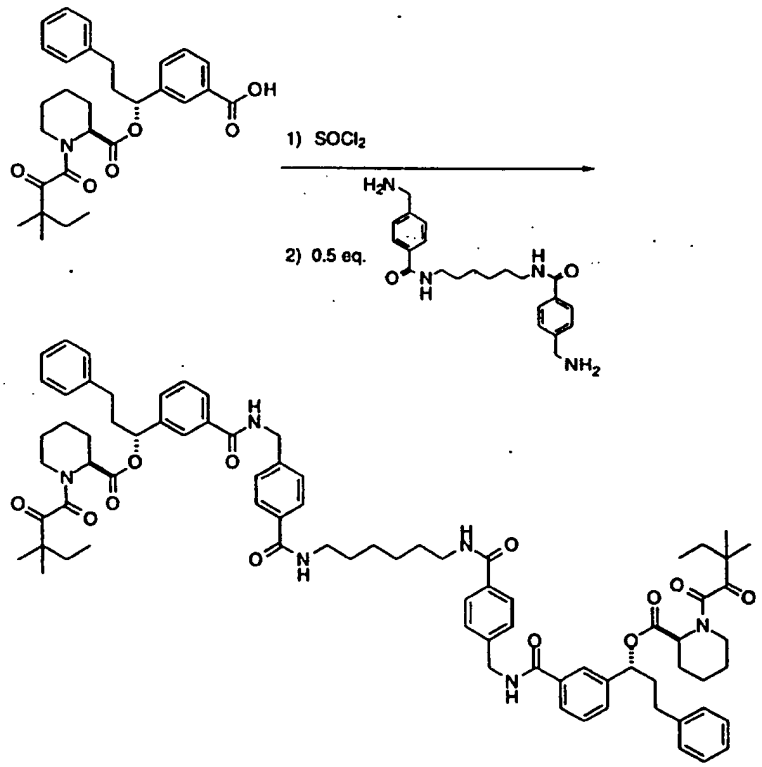




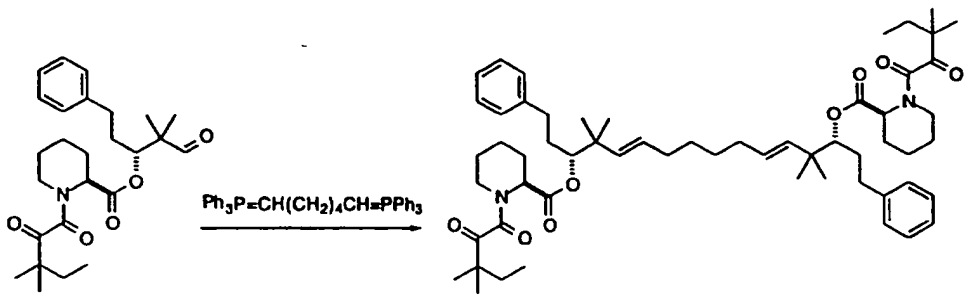
see: Holt, *et al. J. Amer. Chem.. Soc*, **1993**, *115*, 9925-9938.



see: Holt, *et al. J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938.

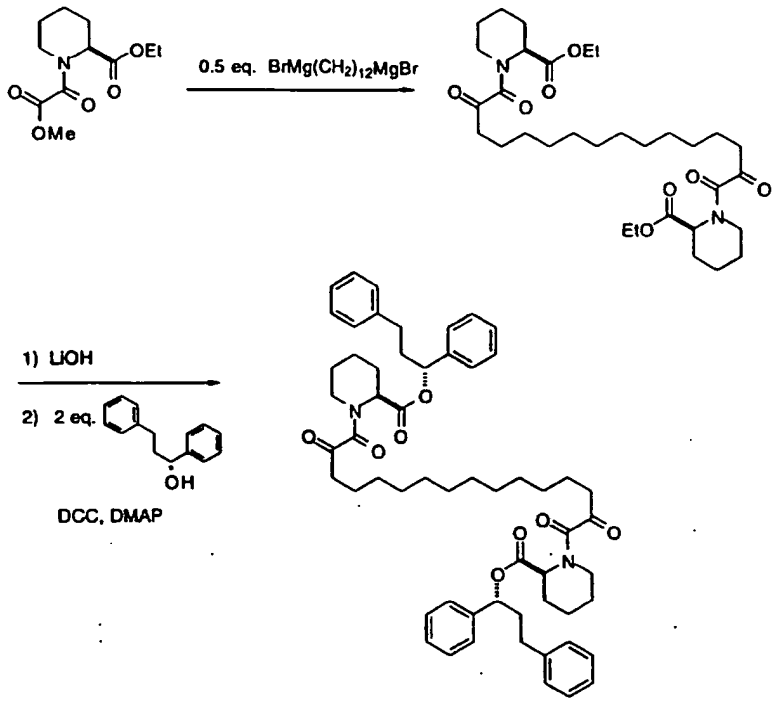


see: Yamashita, et al. *Biomed. Chem. Lett.*, **1993**, *4*, 325-328.



see: Yamashita, et al. *Biomed. Chem. Lett.*, **1993**, *4*, 325-328.

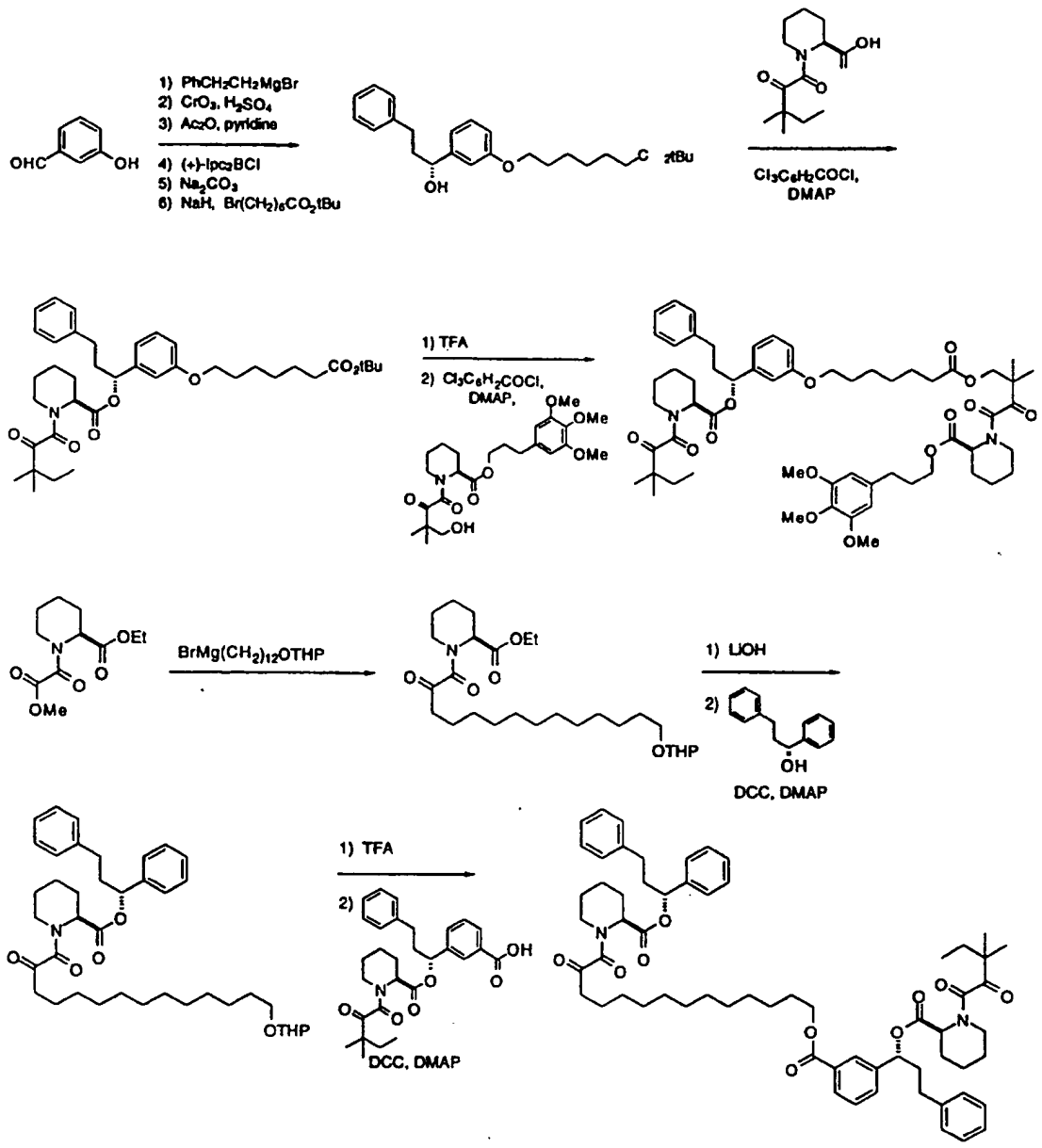
Bis-Wittig reagents are well known in the literature. See e.g., Paquette, *et al.*, *J. Amer. Chem. Soc.*, **1985**, *107*, 6598; Nicolaides, *Synthesis*, **1977**, 127.



see: Holt, *et al. J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938.

Bis-Grignard reagents are also well known in the literature. See e.g., Babudri, *et al. J. Orgmet. Chem.*, **1991**, *405*, 53-58; and Fujisawa *et al. Bull. Chem. Soc. Jpn.*, **1983**, *56*, 345.

Heterodimers (e.g., where $M^1 \neq M^2$) may be prepared by stepwise attachment of each monomer to the linker. Attachment methods may be different for each monomer and the linker may be non-symmetrical and/or differentially functionalized to facilitate stepwise attachment of monomers. By way of example, the following reaction schemes illustrate formation of heterodimers.



Also included in this invention are multimeric variants of formula I compounds wherein three to five formula II monomers are joined using one to four linker moieties, exemplified by but not limited to compounds of formula III and formula IV.

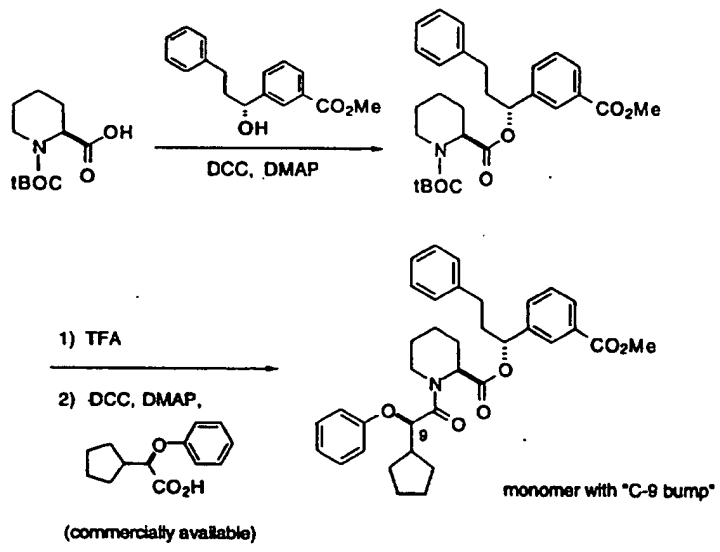
M^1-L-M^2-L'-M^3-L''-M^4 (III)

M^1-L-M^2 I

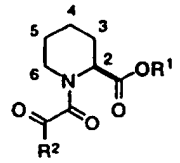
M^3 (IV)

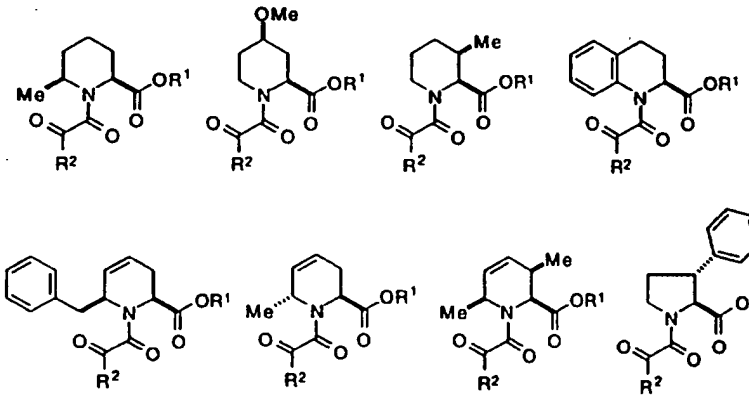
Bumps

This invention also includes compounds containing substituents ("bumps") which diminish, and preferably substantially preclude, their binding to FKBP12 or other native immunophilins but which do bind to mutant FKBPs. Mutant FKBPs may be obtained and screened for binding to a selected multimerizing compound as described in PCT/US94/01617 and PCT/US94/08008. Multimerizing agents containing such bumps permit more selective binding to mutant FKBPs or chimeras containing engineered FKBP domains without interference by indigenous pools of FKBP12, which is desirable for certain applications, especially uses in whole organisms. Preferably the bump-containing monomers and their related multimerizing agents of this invention bind to FKBP12 and/or inhibit rotamase activity of FKBP12 at least about an order of magnitude less than any of FK506, FK520 or rapamycin. Such assays are well known in the art. See *e.g.* Holt *et al., J. Amer. Chem Soc., supra.*. The diminution in inhibitory activity may be as great as about 2 orders of magnitude, and in some cases will exceed about three orders of magnitude. Useful bump substituents include but are not limited to alkyl, aryl, -O-alkyl, -O-aryl, substituted or unsubstituted amine, amide, carbamide and ureas, where alkyl and aryl are as previously defined. See e.g. PCT/US94/01617 and PCT/US94/08008. Monomers containing such substituents , which can be dimerized via linkers and methodology described above, are exemplified in the following synthetic schemes.



Many substituted proline and pipecolic acid derivatives have been described in the literature. Using synthetic procedures similar to those described above, substituted prolines and pipecolates can be utilized to prepare monomers with "bumps" at positions C-2 to C-6 as exemplified below.





For representative examples of substituted prolines and pipecolic acids see:

Chung, *et al.*, *J. Org. Chem.*, **1990**, *55*, 270; Shuman, *et al.*, *J. Org. Chem.*, **1990**, *55*, 738; Hanson, *et al.*, *Tetrahedron Lett.*, **1989**, *30*, 5751; Bailey, *et al.*, *Tetrahedron Lett.*, **1989**, *30*, 6781.

This invention also includes compounds containing structural elements or substituents which enhance binding to mutant FKBPs relative to indigenous FKBPs. Preferably, such compounds bind to mutant FKBPs at least an order of magnitude better than they bind to FKBP12, and in some cases binding to mutant FKBPs will be greater than 3 orders of magnitude better than to FKBP12. For example, such enhancements in binding to mutant FKBPs can be achieved by compounds containing a carboxylic acid or an amine where the mutant FKBP contains a complementary group (histidine/arginine or aspartate/glutamate) in an appropriate location to form a salt bridge between the compound and the mutant FKBP.

Binding affinities of various multimerizing agents of this invention or their component monomers with respect to FKBP or other immunophilin proteins may be determined by adaptation of conventional methods used in the case of FKBP. For instance, the practitioner may measure the ability of a compound of this invention to compete with the binding of a known ligand to the protein of interest. See e.g. Sierkierka et al, 1989, Nature 341, 755-757 (test compound competes with binding of labeled FK506 derivative to FKBP).

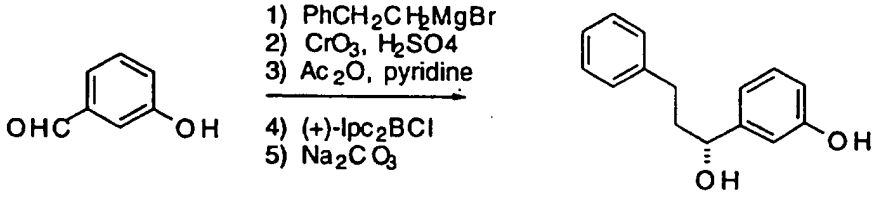
The ability of the multimerizing agents to multimerize chimeric proteins may be measured in cell-based assays by measuring the occurrence of an event triggered by such multimerization. For instance, one may use cells containing and capable of expressing DNAs encoding chimeric proteins comprising one or more immunophilin-derived ligand binding domains and one or more effector domains capable, upon multimerization, of actuating a biological response. We prefer to use cells which further contain a reporter

gene under the transcriptional control of a regulatory element (i.e., promoter) which is responsive to the multimerization of the chimeric proteins. The design and preparation of illustrative components and their use in so engineering cells is described in PCT/US94/01617. The cells are grown or maintained in culture. A multimerizing agent is added to the culture medium and the presence of the reporter gene product is measured. Positive results, i.e., multimerization, correlates with transcription of the reporter gene as observed by the appearance of the reporter gene product.

Examples

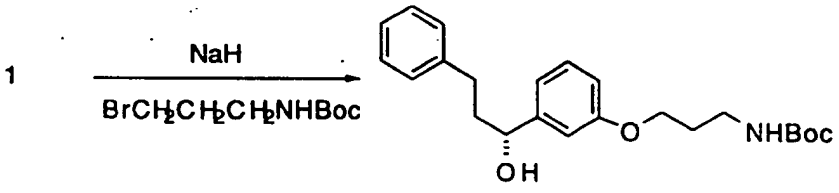
Synthetic Overview, part I:

The synthesis of functionalized chiral alcohols was carried out as follows. The unsubstituted chiral alcohol **1** was prepared from 3-hydroxybenzaldehyde in five steps following reported procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938.

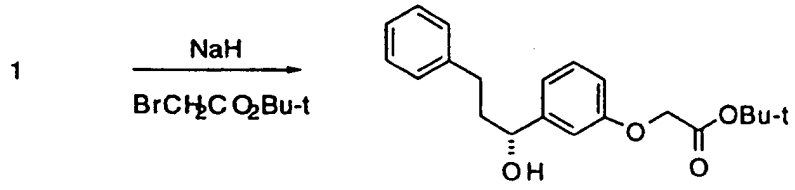


1

Alkylation of **1** with 3-*N*-Boc-aminopropylbromide in the presence of one equivalent of NaH gave **2** in good yield. Similarly, alkylation of **1** with *tert*-butyl bromoacetate provided **3**.

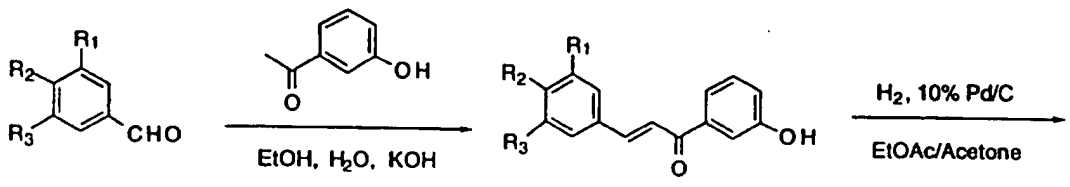


2

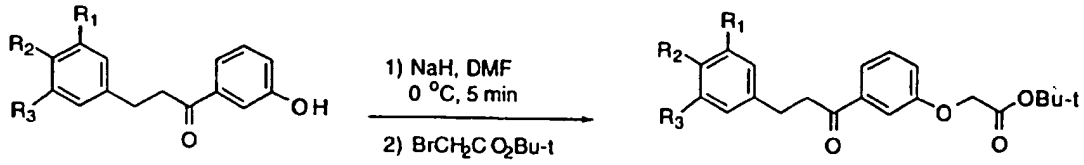


3

Chiral alcohols containing left-phenyl ring substitutions were prepared using a chalcone chemistry as shown in the following scheme.

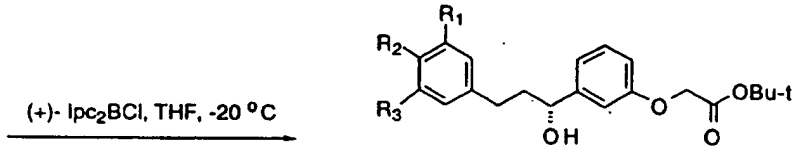


4: $R_1 = R_2 = OCH_3$, $R_3 = H$
5: $R_1 = R_2 = R_3 = OCH_3$
6: $R_1 = R_2 =$ OCH_2O, $R_3 = H$



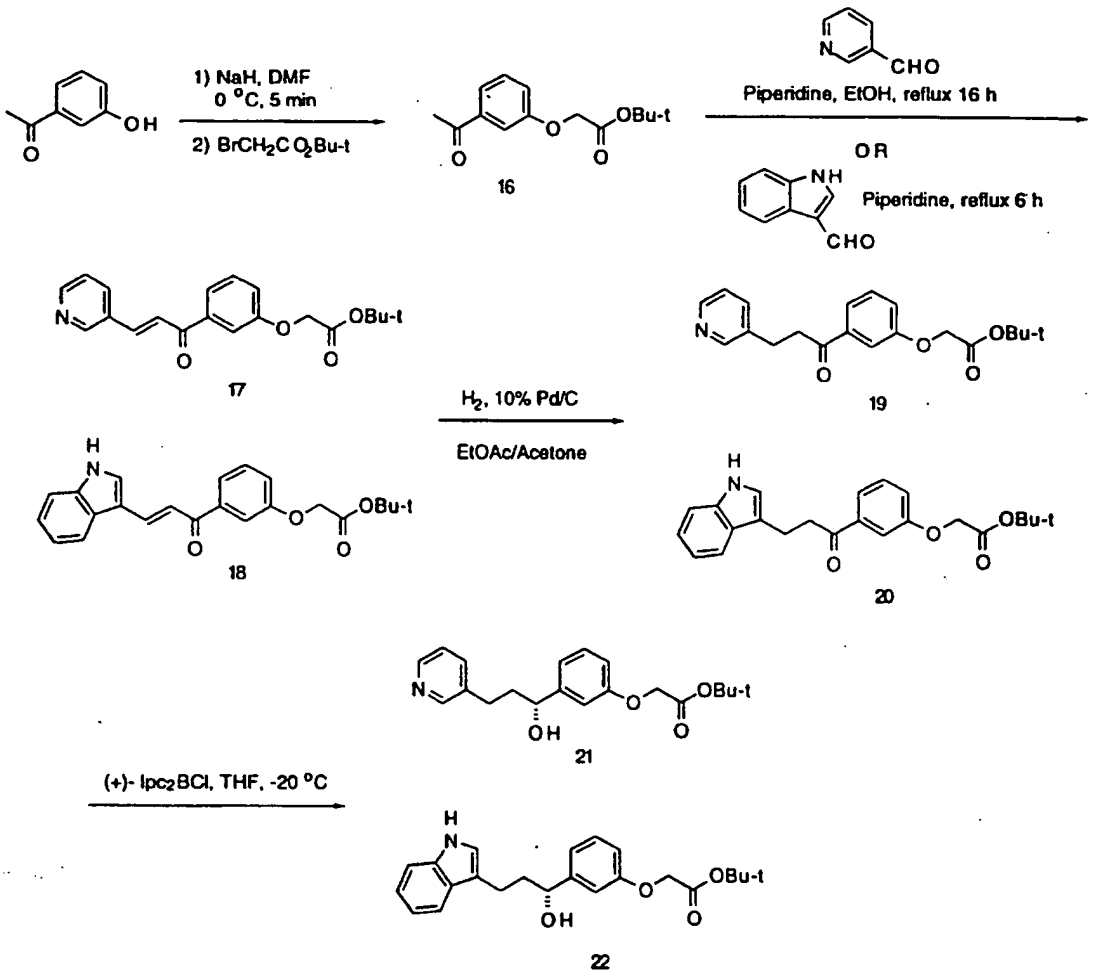
7: $R_1 = R_2 = OCH_3$, $R_3 = H$
8: $R_1 = R_2 = R_3 = OCH_3$
9: $R_1 = R_2 =$ OCH_2O, $R_3 = H$

10: $R_1 = R_2 = OCH_3$, $R_3 = H$
11: $R_1 = R_2 = R_3 = OCH_3$
12: $R_1 = R_2 =$ OCH_2O, $R_3 = H$

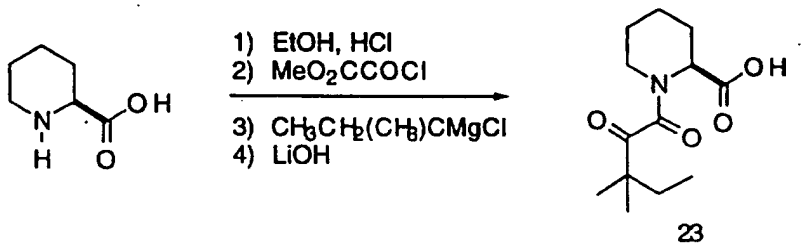


13: $R_1 = R_2 = OCH_3$, $R_3 = H$
14: $R_1 = R_2 = R_3 = OCH_3$
15: $R_1 = R_2 =$ OCH_2O, $R_3 = H$

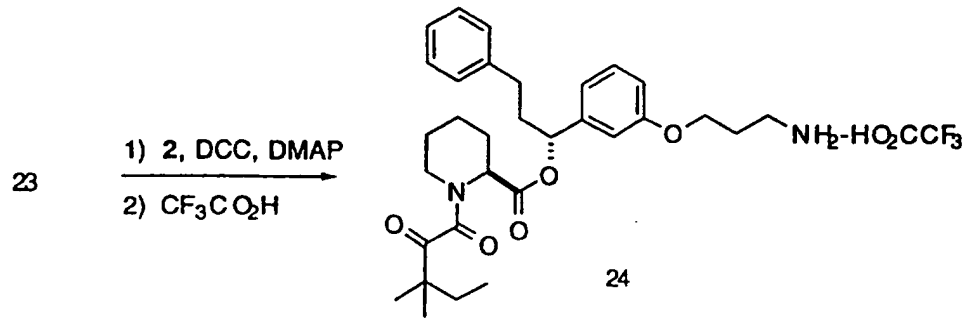
Pyridine and indole containing chiral alcohols were prepared using a similar chalcone chemistry but with some minor modifications as shown below:

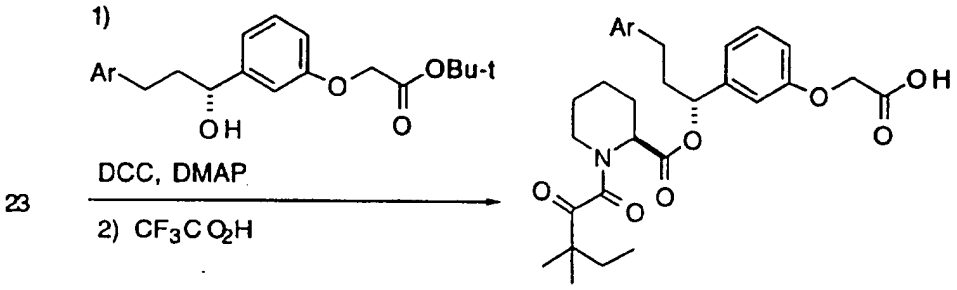


The carboxylic acid **23** was prepared from L-pipecolic acid in four steps following literature procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938.



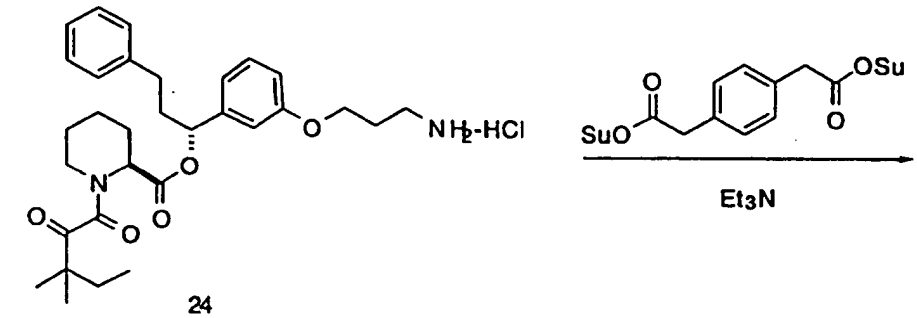
Coupling of **23** with **2** using DCC/DMAP and then removal of Boc-group with trifluoroacetic acid give the amine monomer **24** in good yield. The carboxylic acid monomers **25-30** were produced in a similar fashion.



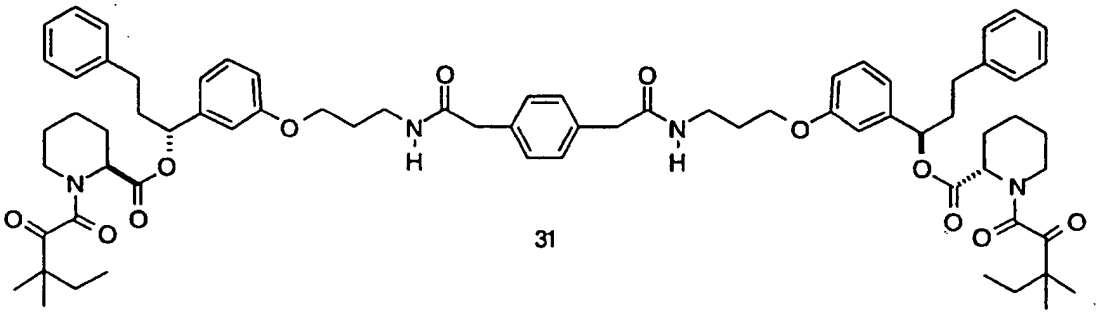


25: Ar = Ph
26: Ar = 3,4,-$(OCH_3)_3$Ph
27: Ar = 3,4,5-$(OCH_3)_3$Ph
28: Ar = 3,4-(OCH_2O)Ph
29: Ar = 3-pyridyl
30: Ar = 3-indolyl

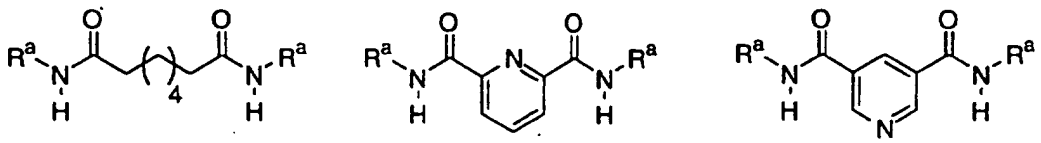
With monomers **24** and **25-30** in hand, various dimers were then synthesized. The amine **24** was treated with disuccinimidyl dicarboxylates to produce dimers **31-34** and **37**, and **38**. Reaction of **24** with benzene-1,3-disulfonyl chloride yielded **36**. Coupling of **24** with triethylene glycol bis(chloroformate) yielded **39**. Treatment of compound **34** with methyl iodide afforded **35** in quantitative yield.



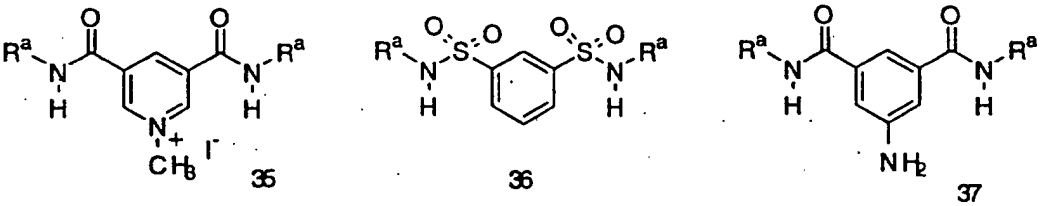
24



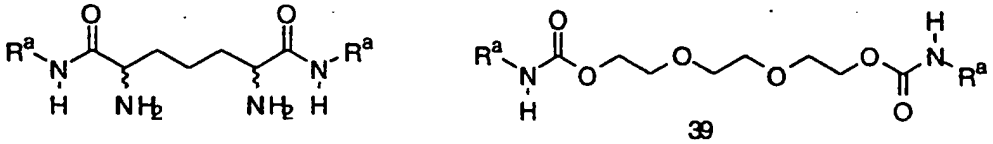
31



32 33 34

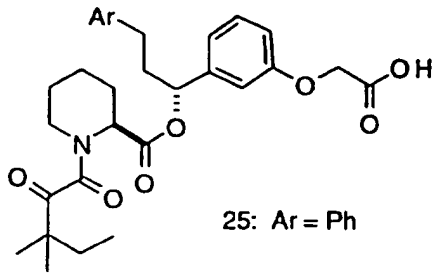


35 36 37

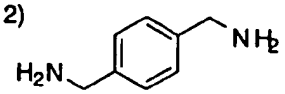


38 39

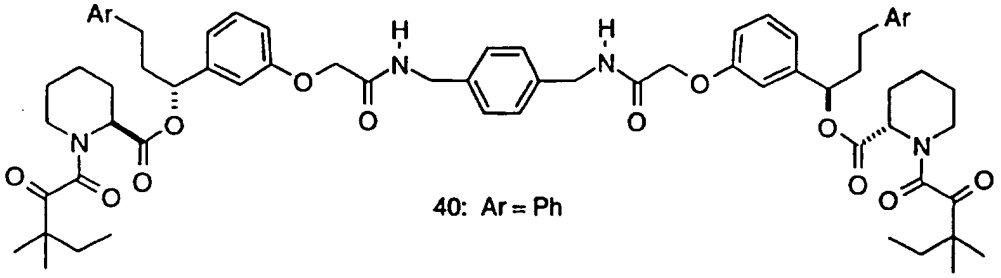
5 The acids **25-30** were converted to their activated succinimidyl esters and then coupled with various diamines to give dimers **40-63**. (R^a and R^b groups represent the various monomers, M).



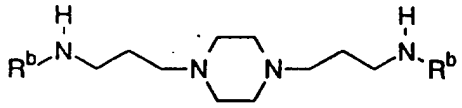
1) DSC, pyridine
2)



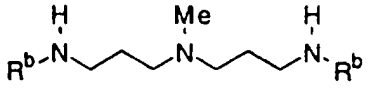
25: Ar = Ph



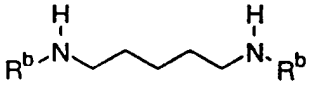
40: Ar = Ph



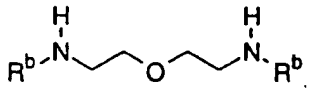
41: Ar = Ph



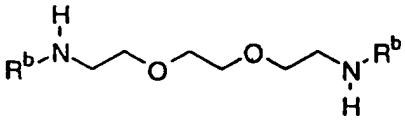
42: Ar = Ph



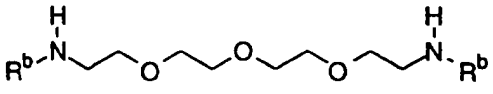
43: Ar = Ph
44: Ar = 3,4-$(OCH_3)_2$Ph
45: Ar = 3,4,5-$(OCH_3)_3$Ph
46: Ar = 3,4-(OCH_2O)Ph
47: Ar = 3-pyridyl



48: Ar = Ph
49: Ar = 3,4-$(OCH_3)_2$Ph
50: Ar = 3,4,5-$(OCH_3)_3$Ph
51: Ar = 3,4-(OCH_2O)Ph
52: Ar = 3-pyridyl



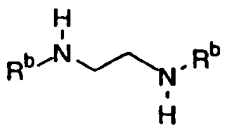
53: Ar = Ph
54: Ar = 3,4-$(OCH_3)_2$Ph
55: Ar = 3,4,5-$(OCH_3)_3$Ph
56: Ar = 3,4-(OCH_2O)Ph
57: Ar = 3-pyridyl
58: Ar = 3-indolyl

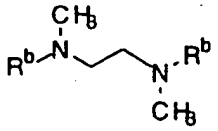


59: Ar = Ph
60: Ar = 3,4-$(OCH_3)_2$Ph
61: Ar = 3,4,5-$(OCH_3)_3$Ph
62: Ar = 3,4-(OCH_2O)Ph
63: Ar = 3-pyridyl

Compounds 64-67, based on the parent structure of 40 but containing the specified linkers and Ar moieties, were made by adaptation of methods described herein.

The structure of the four compounds was confirmed by NMR and MS spectroscopy. All four were found to be active in cell-based transcription assays such as described infra.





64: Ar = 3,4-$(OCH_3)_2$Ph
65: Ar = 3-pyridyl

66: Ar = 3,4-$(OCH_3)_2$Ph
67: Ar = 3-pyridyl

Synthetic Details

General Methods

Proton and carbon magnetic resonance spectra (^1H, ^{13}C NMR) were recorded on Bruker ARX-300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0). All reagents were analytical grade and were used as received. Anhydrous solvents were purchased from Aldrich in sure-seal bottles. Chromatography refers to short column chromatography using TLC grade silica gel 60 G (Merck) and the indicated solvents as the mobile phase. HPLC was conducted using a 4.6 mm x 250 mm Daicel *Chiracel OD* column and (unless otherwise noted) a mobile phase of 85:15 hexane-propanol, flow rate of 1 mL/min, and UV detection at 210 nm. Melting points are uncorrected.

Preparation of Functionalized Chiral Alcohols

(1*R*)-3-Phenyl-1-(3-(3-*tert*-butyloxycarbamylpropyl)oxyphenyl)propan-1-ol (2)

(1*R*)-3-Phenyl-1-(3-hydroxyphenyl)propan-1-ol (1, 98% ee, 1.47 g, 6.45 mmol, prepared in five steps from 3-hydroxybenzaldehyde following reported procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938) was added to a suspension of NaH (60% dispersion in mineral oil, 310 mg, 7.74 mmol) in DMF (30 mL). 3-*tert*-Butyloxycarbamylpropyl bromide (3.07 g, 12.9 mmol) was then added and the resulting mixture was stirred at 40 °C under N_2 overnight. The reaction was quenched with water (50 mL) and the mixture was extracted with EtOAc (250 mL). The organic layer was washed with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo*. The mixture was redissolved in Et_2O (150 mL) and washed with 2 N NaOH (2 x 100 mL) to remove any unreacted 1 (which has the same R_f as the product 2). The organic layer was then washed with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (silica gel, 30% EtOAc/hexanes) afforded 2 (1.9 g, 77% yield, 96% ee by Chiracel HPLC: retention time 19.0 min for the (1*R*)-enantiomer and 15.7 min for the (1*S*)-enantiomer) as

a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.40-6.85 (m, 9 H), 4.76 (t, J = 5.3 Hz, 1 H), 4.12 (t, J = 5.9 Hz, 2 H), 3.42 (t, J = 6.3 Hz, 2 H), 2.80 (m, 2 H), 2.10-1.85 (m, 6 H), 1.53 (s, 9 H), ; ^{13}C NMR ($CDCl_3$, 75MHz) 159.4, 156.4, 146.8, 142.1, 129.9, 128.83, 128.78, 126.2, 118.8, 114.0, 112.4, 74.2, 66.1, 40.8, 32.4, 30.0, 28.8. MS(FAB): $(M+Na)^+$ 408.

(1*R*)-3-Phenyl-1-(3-(2-*tert*-butyloxy-2-oxoethyl)oxyphenyl)propan-1-ol (3)

(1*R*)-3-Phenyl-1-(3-hydroxyphenyl)propan-1-ol (**1**, 98% ee, 1.7 g, 7.46 mmol, prepared in five steps from 3-hydroxybenzaldehyde following reported procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938) was added to a suspension of NaH (60% dispersion in mineral oil, 358 mg, 8.95 mmol) in DMF (50 mL). *tert*-Butyl bromoacetate (2.4 mL, 14.9 mmol) was then added and the resulting mixture was stirred at 40 °C under N_2 overnight. The reaction was quenched with water (50 mL) and the mixture was extracted with EtOAc (250 mL). The organic layer was washed with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (silica gel, 20% EtOAc/hexanes) afforded **3** (1.64 g, 64% yield, 98% ee by Chiracel HPLC: retention time 42.2 min for the (1*R*)-enantiomer and 30.6 min for the (1*S*)-enantiomer) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.22-6.71 (m, 9 H), 4.58 (t, 1 H), 4.44 (s, 2 H), 2.68-2.59 (m, 2 H), 2.05-1.93 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 168.4, 158.6, 146.8, 142.1, 130.0, 128.8, 128.7, 126.2, 119.5, 114.1, 112.6, 82.7, 74.1, 66.1, 40.8, 32.4, 28.4. HRMS(FAB): $(M+Na)^+$ calcd 365.1729, found 365.1721.

3,4- Dimethoxy-3'- hydroxy chalcone (4)

A solution of 3,4-Dimethoxybenzaldehyde (16.6 g, 100 mmol) in EtOH (75 mL) was treated with 3-Hydroxyacetaphenone (13.6 g, 100 mmol) and the resulting solution cooled to 0 °C in an ice bath. A 200 mL solution of aqueous KOH (28 g, 500 mmol) was added slowly and the resulting bright red solution was allowed to stir overnight (16 h) at room temperature. The mixture was then acidified to pH 5 by the dropwise addition of concentrated HCl and the resulting suspension extracted with EtOAc (2 x 200 mL). The combined organic extract was washed with a saturated NaCl solution (2 x 100 mL), dried over $MgSO_4$, filtered, evaporated, and flash chromatographed (silica gel, 30% → 50% EtOAc/hexanes) to give crude material. The crude solid was crystallized from EtOAc to afford 13.9 g (49%) of a yellow colored solids: IR (neat) 3420, 1650, 1575, 1510, 1265, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.80 (d, J = 15.6 Hz, 1H), 7.68 (s, 1H), 7.59, (d, J= 7.7 Hz, 1H), 7.42-7.36 (m, 2H), 7.24 (dd, J = 8.3, 1.8 Hz, 1H), 7.16-7.13 (m, 2H), 6.90 (d, J = 8.3 Hz, 1H), 6.82 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 191.3. 157.0, 152.0, 149.7, 146.1, 140.1, 130.2, 128.2, 123.8, 121.2, 120.7, 120.3, 115.7, 111.6, 110.7, 56.4.

3,4,5- Trimethoxy-3'- hydroxy chalcone (5)

Prepared in a similar manner as (4) from 3,4,5- trimethoxybenzaldehyde. Flash chromatography (silica gel, 30% → 50% EtOAc/hexanes) afforded 2.61 g (17%) of yellow colored solids: ^{1}H NMR ($CDCl_3$, 300 MHz) 9.80 (s, 1H), 7.82 (d, J = 15.6 Hz, 1H), 7.70-7.63 (m, 2H), 7.48 (s, 1H), 7.39 (app t, J = 7.9 Hz, 1H) 7.23 (s, 2H) 7.08 (d, J = 7.6 Hz, 1H), 3.87 (s, 6H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 189.5, 158.1, 153.5, 144.7, 140.1, 139.5, 130.6, 130.1, 121.8, 120.5, 119.9, 115.0, 106.9, 60.5, 56.5.

3'- Hydroxy- 3,4-methylenedioxy chalcone (6)

Prepared in a similar manner as (4) from piperonal. Crude solids (26.7 g, 100%) were carried on directly to the next reaction step without chromatographic purification or characterization.

3-(3,4- Dimethoxyphenyl)-1- (3-hydroxyphenyl)propan-1-one (7)

A solution of 3,4- Dimethoxy-3'- hydroxy chalcone (4) (10 g, 35.2 mmol) in a 1:1 mixture of EtOAc:Acetone (40mL) was treated with 10% Pd on Carbon (500 mg) and the mixture hydrogenated at 40-50 psi pressure of H_2 for 3 h. The reaction mixture was filtered through a pad of Celite with the aid of acetone and the filtrate concentrated to afford a crude solid. The crude solid was triturated with EtOAc and filtered to afford 7.83 g (78%) of white solids which proved to be of ~90% purity by ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.56 (s, 1H), 7.55, (d, J= 2.2 Hz, 1H), 7.53-7.33 (m, 1H), 7.10 (dd, J = 7.9, 2.4 Hz, 1H), 6.80-7.79 (m, 3H), 6.61 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.28 (t, J = 7.9 Hz, 2H), 3.02 (t, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 200.6, 156.9, 149.3, 147.8, 138.6, 134.2, 130.3, 121.1, 120.6, 115.0, 112.4, 111.8, 56.3, 41.2, 30.3.

1-(3-Hydroxyphenyl)-3- (3,4,5-trimethoxyphenyl)propan-1-one (8)

Prepared in a similar manner as (7) from 3,4,5- Trimethoxy-3'- hydroxy chalcone (5). Flash chromatography (silica gel, 40% → 50% EtOAc/hexanes) of crude material afforded 1.37 g (68%) of white solids: IR (neat) 3395, 2940, 1680, 1590, 1505, 1455, 1240, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.54-7.52 (m, 2H), 7.34 (app t, J = 8.1 Hz, 1H), 7.10 (dd, J= 7.9, 2.2 Hz, 1H), 6.48 (s, 2H), 6.08 (s, 1H), 3.85 (s, 9H), 3.30 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 200.0, 156.7, 153.6, 138.7, 137.4, 136.7, 130.3, 120.9, 115.0, 105.8, 61.3, 56.5, 41.0, 31.0.

1-(3-Hydroxyphenyl)-3- (3,4-methylenedioxyphenyl)propan-1-one (**9**)

Prepared in a similar manner as (**7**) from 3'- Hydroxy- 3,4-methylenedioxy chalcone (**6**). Crystallization of crude material from EtOAc/hexanes afforded 4.10 g (41%) of white solids: ^{1}H NMR ($CDCl_3$, 300 MHz) 9.73 (s, 1H), 7.43 (d, J= 7.8 Hz, 1H), 7.34-7.29 (m, 2H), 7.02 (dd, J = 8.0 Hz, 1H), 6.88 (m, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 5.96 (s, 2H), 3.26 (t, J = 7.6 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.4 158.0, 147.5, 145.7, 138.4, 135.4, 130.1, 121.5, 120.5, 119.3, 114.4, 109.2, 108.4, 101.0, 40.2, 29.7.

1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (**10**)

A 60% mineral oil suspension of NaH (279 mg, 6.98 mmol) in anhydrous DMF (10 mL) was cooled to 0 °C in an ice bath and solid 3-(3,4- Dimethoxyphenyl)-1- (3-hydroxyphenyl)propan-1-one (**7**) (2 g, 6.98 mmol) added in one portion. The resulting yellow solution was stirred for 5 min after which time *tert*-butylbromoacetate (1.18 mL, 7.33 mmol) was added. Stirring was continued at 0 °C for 15 min after which time the reaction mixture was warmed to room temperature and partitioned between diethyl ether (50 mL) and water (50 mL). The organic layer was washed with a saturated NaCl solution (2 x 50 mL), dried over $MgSO_4$, filtered, evaporated, and flash chromatographed (silica gel, 30% EtOAc/hexanes) to afford 2.30g (82%) of a clear colorless oil: IR (neat) 2980, 1750, 1685, 1590, 1515, 1260, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.59 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.39 (app t, J = 8.0 Hz, 1H), 7.14 (dd, J = 8.2, 2.6 Hz, 1H), 6.81-6.79 (m, 3H), 4.58 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.28 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.8 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 199.2, 168.0, 158.6, 149.3, 147.8, 138.7, 134.2, 130.1, 121.8, 120.6, 113.5, 112.2, 111.8, 108.1, 83.0, 66.1, 56.2, 41.1, 30.2, 28.4.

1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4,5-trimethoxyphenyl)propan-1-one (**11**)

Prepared in a similar manner as (**10**) from 1-(3-Hydroxyphenyl)-3- (3,4,5-trimethoxyphenyl)propan-1-one (**8**). Flash chromatography (silica gel, 30% → 40% EtOAc/hexanes) of crude material afforded 1.30 g (96%) of a clear colorless oil: IR (neat) 2955, 1750, 1684, 1590, 1455, 1230, 1150, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.59 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.39 (app t, J = 7.9 Hz, 1H), 7.14 (dd, J = 8.2, 2.6 Hz, 1H), 6.47 (s, 2H), 4.58 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.28 (t, J = 7.3 Hz, 2H), 3.01 (t, J = 7.8 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 75MHz) 199.1 168.0, 158.5, 153.6, 138.6, 137.4 136.8, 130.1, 121.8, 120.4, 113.6, 105.8, 83.0, 66.1, 61.2, 56.5, 41.0, 31.0, 28.4.

1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-methylenedioxyphenyl)propan-1-one (**12**)

Prepared in a similar manner as (**10**) from 1-(3-Hydroxyphenyl)-3- (3,4-methylenedioxyphenyl)propan-1-one (**9**). Flash chromatography (silica gel, 20% → 30% EtOAc/hexanes) of crude material afforded 5.04 g (89%) of a clear colorless oil: IR (neat) 2980, 1750, 1685, 1490, 1445, 1245, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.58 (dd, J = 6.7, 1.1 Hz, 1H), 7.48 (s, 1H), 7.39 (app t, J = 8.0 Hz, 1H), 7.17-7.13 (m, 1H), 6.89-6.69 (m, 4H), 5.94 (s, 2H), 4.58 (s, 2H), 3.25 (t, J = 7.8 Hz, 2H), 2.99 (t, J = 7.8 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75MHz) 199.0 168.0, 158.5, 148.1, 146.3, 138.6, 135.4, 130.1, 121.8, 121.5, 120.6, 113.4, 109.3, 108.7, 101.2, 83.0, 66.1, 41.1, 20.3, 28.4.

(R) 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-ol (**13**)

A solution of 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-dimethoxyphenyl)propan-1-one (**10**) (3.0 g, 7.49 mmol) in THF (5 mL) at -20 °C was treated with a solution of (+)-B-chlorodiisopinocamphenylborane (2.9 g, 8.99 mmol) in THF (10 mL) at -20 °C. The resulting mixture was allowed to stand in a -20 °C freezer for 48 h after which time the mixture was evaporated and treated with diethyl ether (25 mL) followed by diethanolamine (8 mL). The viscous mixture was allowed to stir at room temperature for 3 h, after which time, was filtered through a pad of Celite with the aid of diethyl ether. The cloudy filtrate was evaporated and flash chromatographed (silica gel, 30% → 40% EtOAc/hexanes) to afford 2.72 g (90%) of a clear colorless oil. (95% ee by Chiracel HPLC, 25% i-PrOH/hexanes, retention time 44.4 min for the *R*-enantiomer and 35.7 min for the *S*-enantiomer): IR (neat) 3525, 2935, 1750, 1515, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.30 -7.25 (m, 2H), 6.99-6.73 (m, 5H), 4.68 (m, 1H), 4.53 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.72-2.63 (m, 2H), 2.12-1.97 (m, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.4, 158.5, 149.3, 147.6, 146.9, 134.8, 130.0, 120.6, 119.5, 114.0, 112.6, 112.2, 111.7, 82.7, 74.1, 66.1, 56.3, 56.2, 41.0, 32.0, 28.4.

(1*R*)-3-(3,4,5-Trimethoxyphenyl)-1-(3-(tert-butoxycarbonylmethoxy)phenyl)-propan-1-ol (**14**)

To a solution of **11** (1.30 g, 3.0 mmol) in THF (5 mL) at -23 °C under N_2 was added a cold (-23 °C) solution of (+)-*B*-chlorodiisopinocampheylborane (1.64 g, 5.1 mmol) in THF (10 mL). The mixture was placed in a freezer for 3 days. Then, the mixture was concentrated *in vacuo* and the residue was redissolved in diethyl ether (60

mL). The ether solution was treated with diethanolamine (0.86 mL, 9.0 mmol) with vigorous stirring at room temperature for 3 h. The white precipitates were filtered off and the filtrate was concentrated *in vacuo*. Chromatography on silica (50-100% EtOAc/hexanes) provided 1.3 g (99%) of a colorless oil (98.1% ee by Chiracel HPLC, 20% i-PrOH/hexanes, retention time 46.4 min for the *R*-enantiomer and 40.0 min for the *S*-enantiomer). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (t, J = 7.8 Hz, 1 H), 6.96 (m, 2 H), 6.82 (m, 1 H), 6.41 (s, 2 H), 4.69 (t, J = 6.2 Hz, 1 H), 4.52 (s, 2 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 2.65 (m, 2 H), 2.05 (m, 2 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 168.4, 158.6, 153.5, 146.8, 137.9, 136.6, 130.0, 119.5, 114.0, 112.7, 105.7, 82.8, 74.1, 66.0, 61.2, 56.5, 40.8, 32.8, 28.4.

(R) 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-methylenedioxyphenyl)propan-1-ol (**15**)

Prepared in a similar manner as (**13**) from 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-methylenedioxyphenyl)propan-1-one (**12**). Flash chromatography (silica gel, 20% → 25% EtOAc/hexanes) of crude material afforded 3.84g (96%) of a clear colorless oil: IR (neat) 3440, 1750, 1490, 1440, 1245, 1150, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.30-7.24 (m, 1 H),6.98-6.93 (m, 2H), 6.82 (dd, J = 8.2, 2.5 Hz, 1H), 6.75-6.64 (m, 3H), 5.93 (s, 2H), 4.67-4.63 (m, 1H), 4.53 (s, 2H), 2.68-2.60 (m, 2H), 2.10-1.95 (m, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75MHz) 168.4, 158.5, 148.0, 146.9, 146.0, 136.0, 130.0, 121.5, 119.5, 114.1, 112.5, 109.3, 108.5, 101.1, 82.7, 73.9, 66.1, 41.1, 32.1, 28.4.

3'-(*tert*-Butoxycarbonylmethoxy)acetophenone (**16**)

To a suspension of NaH (60% dispersion in mineral oil, 1.47 g, 36.7 mmol) in anhydrous DMF (50 mL) at 0 °C was added solid 3'-hydroxyacetophenone (5.0 g, 36.7 mmol). The mixture was stirred under N_2 for 10 min and a clear yellow solution was formed. Then, *tert*-butylbromoacetate (6.23 mL, 38.5 mmol) was added and the mixture stirred at 0 °C for 5 min and then at room temperature for 20 min. TLC showed no starting material remaining. The mixture was partitioned between EtOAc (250 mL) and water (100 mL). The organic layer was separated, washed with saturated brine, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (20% EtOAc/hexanes) gave 7.6 g (83%) of a white crystal. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.60-7.14 (m, 4 H), 4.59 (s, 2 H), 2.60 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 198.0, 168.0, 158.6, 138.9, 130.1, 122.3, 120.6, 113.5, 83.0, 66.1, 28.4, 27.0.

3-(3-Pyridyl)-1-(3-(tert-butoxycarbonylmethoxy)phenyl)-2-propen-1-one (17)

A mixture of **16** (4.0 g, 16 mmol), nicotinaldehyde (1.89 mL, 20 mmol), and piperidine (4.0 mL, 40 mmol) in absolute EtOH (65 mL) was heated at reflux for 16 h. The mixture was cooled and concentrated *in vacuo*. Chromatography on silica gel (30-60% EtOAc/hexanes) gave a mixture of unreacted nicotinaldehyde and **17** (both have the same R_f on TLC). Washing of the mixture with hexane in a filter funnel provide 1.73 g (32%) of pure **17** as a yellow crystal. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.87 (d, J = 2.1 Hz, 1 H), 8.66 (dd, J = 4.8, 1.5 Hz, 1 H), 7.97 (d, J = 7.9 Hz, 1 H), 7.80 (d, J = 16.7 Hz, 1 H), 7.66 (d, J = 7.6 Hz, 1 H), 7.60 (d, J = 15.9 Hz, 1 H), 7.55 (s, 1 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.38 (dd, J = 7.9, 4.8 Hz, 1 H), 7.20 (dd, J = 8.2, 2.6 Hz, 1 H), 4.62 (s, 2 H), 1.52 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 189.7, 175.0, 168.0, 158.7, 151.6, 150.5, 141.4, 139.5, 134.9, 131.0, 130.2, 124.2, 122.3, 120.6, 114.1, 83.1, 66.2, 28.4.

1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3-indoyl)-2-propen-1-one (18)

A mixture of **16** (2.0 g, 8.0 mmol) and 3-indolecarboxaldehyde (967 mg, 6.66 mmol) in piperidine (4mL) was heated at reflux for 6 h. The reaction mixture was cooled and treated with pH 7 phosphate buffer (25 mL) and EtOAc (50 mL). The organic portion was washed with a saturated $NaHCO_3$ solution (2 x 50 mL) followed by a saturated NaCl solution (2 x 25 mL) solution. The organic layer was then dried over $MgSO_4$, filtered, evaporated, and flash chromatographed (silica gel, 50% EtOAc/hexanes) to afford 1.47 g (59%) of yellow solids. IR (neat) 1730, 1650, 1560, 1240, 1150 cm^{-1}; ^{1}H NMR (MeOH, 300 MHz) 8.06 (d, J = 15.5 Hz, 1 H), 7.94-7.91 (m, 1 H), 7.76 (s, 1H), 7.62 (dd, J = 6.7, 1.1 Hz, 1H), 7.52-7.42 (m, 4H), 7.40-7.17 (m, 3H), 4.61 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (MeOH, 75 MHz) 192.9, 170.5, 160.2, 142.4, 142.1, 139.8, 134.2, 131.3, 127.2, 124.5, 123.0, 121.7, 120.7, 117.4, 115.3, 113.7, 84.0, 67.2, 28.7.

3-(3-Pyridyl)-1-(3-(tert-butoxycarbonylmethoxy)phenyl)-propan-1-one (19)

A mixture of **17** (1.70 g, 5.0 mmol) and 10% Pd/C (85 mg) in EtOAc (70 mL) was hydrogenated in a Parr under H_2 at 42 psi for 15 h. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Chromatography on silica (50-60% EtOAc/hexanes) gave 1.70 g (100%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.54 (d, J = 2.0 Hz, 1 H), 8.48 (dd, J = 4.8, 1.5 Hz, 1 H), 7.70-7.10 (m, 6 H) 4.58 (s, 2 H), 3.31 (t, J = 7.3 Hz, 2 H), 3.09 (t, J = 7.4 Hz, 2 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 198.3, 168.0, 158.6, 150.4, 148.1, 138.4, 136.9, 136.4, 130.2, 123.7, 121.8, 120.7, 113.5, 83.0, 66.1, 40.2, 28.4, 27.5.

1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3-indoyl)propan-1-one (**20**)

Prepared in a similar manner as (**19**) from 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3-indoyl)-2-propen-1-one (**18**). Flash chromatography (silica gel, 20% → 30% EtOAc/hexanes) afforded 468 mg (80%) of a white solid: IR (neat) 1735, 1680, 1230, 1150 cm^{-1}; ^1H NMR (MeOH, 300 MHz) 7.60-7.55 (m, 2 H), 7.43-7.32 (m, 3H), 7.16-6.99 (m, 4H), 4.57 (s, 2H), 3.39-3.32 (obs t, 2H), 3.16 (t, J = 7.2 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (MeOH, 75 MHz) 202.5, 170.4, 160.0, 140.2, 138.6, 131.3, 129.0, 123.5, 122.9, 122.7, 121.5, 120.0, 119.7, 115.6, 114.6, 112.6, 84.0, 67.1, 41.0, 28.7, 21.6.

(1*R*)-3-(3-Pyridyl)-1-(3-(tert-butoxycarbonylmethoxy)phenyl)-propan-1-ol (**21**)

To a solution of **19** (1.70 g, 4.98 mmol) in THF (10 mL) at -23 °C under N_2 was added a cold (-23 °C) solution of (+)-B-chlorodiisopinocamphenylborane (3.2 g, 9.97 mmol) in THF (20 mL). The mixture was placed in a freezer for 3 days. Then, the mixture was concentrated *in vacuo* and the residue was redissolved in diethyl ether (100 mL). The ether solution was treated with diethanolamine (1.44 mL, 15.0 mmol) with vigorous stirring at room temperature for 3 h. The white precipitates were filtered off and the filtrate was concentrated *in vacuo*. Chromatography on silica (50-100% EtOAc/hexanes) provided 1.41 g (82%) of a colorless oil (97.5% ee by Chiracel HPLC, 25% i-PrOH/hexanes, retention time 78.5 min for the *R*-enantiomer and 52.1 min for the *S*-enantiomer). ^1H NMR ($CDCl_3$, 300 MHz) 8.42 (m, 2 H), 7.55-6.80 (m, 6 H), 4.65 (dd, J = 7.8, 5.1 Hz,1 H), 4.52 (s, 2 H), 2.75 (m, 2 H), 2.05 (m, 2 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75MHz) 175.1, 168.4, 158.6, 150.3, 147.7, 146.8, 137.5, 136.3, 130.0, 123.7, 119.4, 114.1, 112.5, 108.0, 82.8, 73.5, 66.0, 40.5, 29.5, 28.4.

(R) 1-(3-(tert-Butoxycarbonylmethoxy)phenyl)-3-(3-indoyl)propan-1-ol (**22**)

Prepared in a similar manner as (**21**) from 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3-indoyl)propan-1-one (**20**). Flash chromatography (silica gel, 20% → 30% EtOAc/hexanes) afforded 258 mg (55%) of yellowish oil (+95% ee by Chiracel HPLC, 20% i-PrOH/hexanes, retention time 54.2 min for the *R*-enantiomer and 50.7 min for the *S*-enantiomer): IR (neat) 3410, 2930, 1735, 1455, 1230, 1150, 1080 cm^{-1}; ^1H NMR (MeOH, 300 MHz) 7.51 (d, J = 7.8 Hz, 1 H), 7.33 (d, J = 8.1, 1H), 7.25 (app t, J = 7.9, 1H), 7.11-6.92 (m, 5H), 6.82-6.78 (m, 1H), 4.67 (t, J = 5.8 Hz, 1H), 4.54 (s, 2H), 2.85-2.77 (m, 2H), 2.18-2.06 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (MeOH, 75 MHz) 170.8, 159.9, 148.9, 138.6, 130.8, 129.2, 123.2, 122.6, 120.8, 119.9, 116.4, 114.9, 113.7, 112.6, 83.8, 75.0, 67.0, 41.3, 28.7, 22.9.

Preparation of Functionalized Monomers

(1*R*)-3-Phenyl-1-[3-((3-aminopropyl)oxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate trifluroacetic acid salt (**24**)

A solution of alcohol **2** (385 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 255 mg, 1.0 mmol, prepared from L-pipercolic acid in 4 steps following literature procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938), followed by 1,3-dicyclohexylcarbodiimide (DCC, 247 mg, 1.2 mmol), and 4-(dimethylamino)-pyridine (DMAP, 85 mg, 0.70 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir overnight. The mixture was then filtered through glass wool and chromatographed (silica gel, 20% EtOAc/hexanes) to give (1*R*)-3-Phenyl-1-[3-9(3-*tert*-butyloxycarbamylpropyl)oxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (524 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.90 (m, 9 H), 5.80 (t, J = 5.9 Hz, 1 H), 5.32 (d, J = 5.0 Hz, 0.82 H, pipercolate α-H of rotamer A), 4.80 (br. s, 1 H), 4.02 (t, J = 6.1 Hz, 2 H), 3.40-3.25 (m, 3 H), 3.12 (td, J = 13.0, 3.3 Hz, 1 H), 2.60 (m, 2 H), 2.35 (d, J = 14 Hz, 1 H), 2.28 (m, 1 H), 2.07 (m, 1 H), 1.96 (t, J = 6.3 Hz, 2 H), 1.80-1.60 (m, 5 H), 1.43 (s, 9 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.1, 167.6, 159.4, 156.4, 141.7, 141.3, 130.1, 128.9, 128.7, 126.5, 119.4, 114.7, 113.2, 113.0, 66.1, 57.1, 51.7, 47.1, 44.5, 38.3, 32.9, 32.1, 30.0, 28.8, 26.8, 25.4, 24.9, 24.0, 23.8, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 645, $(M+H)^+$ 623.

A solution of the above compound (200 mg, 0.32 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **24** (203 mg, 100%) as a colorless gum: ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.90 (br. s, 3 H), 7.30-6.70 (m, 9 H), 5.70 (t, J= 5.4 Hz, 1 H), 5.23 (d, J = 4.8 Hz, 1 H), 4.01 (m, 2 H), 3.30 (d, J = 12.8 Hz, 1 H), 3.13 (m, 3 H), 2.58 (m, 2 H), 2.40-2.00 (m, 4 H), 1.75-1.50 (m, 5 H), 1.35 (m, 2 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 0.80 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.4, 175.3, 175.2, 170.1, 167.8, 158.8, 142.0, 141.2, 130.2, 128.9, 128.7, 126.5, 119.8, 114.6, 113.0, 108.0, 66.1, 51.8, 47.1, 44.6, 38.6, 38.3, 32.8, 32.1, 27.3, 26.8, 25.3, 23.8, 23.4, 21.5, 9.0. HRMS(FAB): $(M+Na)^+$ calcd: 523.3172 found: 523.3162.

(1*R*)-3-Phenyl-1-(3-(hydroxycarbonylmethoxy)phenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (25)

A solution of alcohol **3** (342 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 255 mg, 1.0 mmol, prepared from L-pipecolic acid in 4 steps following literature procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938), followed by 1,3-dicyclohexylcarbodiimide (DCC, 247 mg, 1.2 mmol), and 4-(dimethylamino)-pyridine (DMAP, 85 mg, 0.70 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir overnight. The mixture was then filtered through glass wool and chromatographed (silica gel, 20% EtOAc/hexanes) to give (1*R*)-3-Phenyl-1-(3-(*tert*-butoxycarbonylmethoxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (470 mg, 82%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.50-6.90 (m, 9 H), 5.93 (t, J = 6.0 Hz, 1 H), 5.46 (d, J = 3.4 Hz, 0.83 H, pipercolate α-H of rotamer A), 4.67 (s, 2 H), 3.50 (d, J = 12.9 Hz, 1 H), 3.32 (td, J = 12.5, 3.0 Hz, 1 H), 2.75 (m, 2 H), 2.53 (d, J = 13.6 Hz, 1 H), 2.41 (m, 1 H), 2.22 (m, 1 H), 2.97-2.71 (m, 6 H), 1.62 (s, 9 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.03 (t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 175.0, 170.0, 168.0, 167.5, 158.5, 141.7, 141.2, 130.2, 128.9, 128.7, 126.5, 120.2, 114.7, 113.6, 82.8, 66.1, 51.6, 47.1, 44.5, 38.2, 32.9, 32.0, 28.4, 26.8, 25.3, 24.0, 23.4, 21.6, 9.2. HRMS(FAB): $(M+Na)^+$ calcd: 602.3094, found: 602.3090.

A solution of the above *tert*-butyl ester (200 mg, 0.34 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **25** (177 mg, 99%) as a colorless gum: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.30-6.80 (m, 9 H), 5.75 (m, 1 H), 5.30 (d, J = 4.8 Hz, 1 H), 4.66 (s, 2 H), 3.35 (d, J = 9.27 Hz, 1 H), 3.19 (td, J = 12.4, 2.9 Hz, 1 H), 2.69 (m, 2 H), 2.39 (d, J = 16.2 Hz, 1 H), 2.30 (m, 1 H), 2.10 (m, 1 H), 1.90-1.60 (m, 6 H), 1.50 (m, 1 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 0.85 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.0, 172.3, 169.8, 167.9, 158.2, 142.2, 141.1, 130.2, 128.9, 128.7, 126.5, 120.3, 115.5, 111.8, 65.5, 57.2, 52.0, 47.2, 44.6, 38.3, 33.0, 32.9, 32.1, 27.0, 25.3, 25.2, 23.9, 23.4, 21.5, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 546.2468, found: 546.2461.

(1*R*)-3-(3,4-Dimethoxyphenyl)-1-[3-(hydroxycarbonylmethoxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (26)

A solution of (R) 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-dimethoxyphenyl) propan-1-ol (**13**) (805 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C was

treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 511mg, 2.0 mmol, prepared from L-pipecolic acid in 4 steps following literature procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938) followed by 4-(dimethylamino)pyridine (DMAP 1 mg) and 1,3-dicyclohexyl carbodiimide (DCC, 413 mg, 2 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir for 2 h then diluted with diethyl ether (20 mL). The reaction mixture was then filtered, evaporated, and flash chromatographed (silica gel, 25% → 30% EtOAc/hexanes) to afford 993 mg (78%) of a clear colorless viscous oil: IR (neat) 2940, 1735, 1645, 1515, 1455, 1225, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.20-7.17 (m, 2H), 6.91-6.69 (m, 5H), 5.73-5.68 (m, 1H). 5.24 (br s, 1H), 4.46 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.29 (br d, J = 13.2 Hz, 1H), 3.07 (td, J = 12.7, 3.0 Hz, 1H), 2.52-2.44 (m, 2H), 2.29 (br d, J = 13.6 Hz, 1H), 2.20-2.13 (m, 1H), 2.04-1.95 (m, 1H), 1.71-1.51 (m, 7H), 1.41 (s, 9H), 1.16, (s, 3H), 1.14 (s, 3H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.2, 170.1, 168.3, 167.6, 158.5, 149.3, 147.8, 141.8, 133.9, 130.1, 120.5, 120.3, 114.7, 113.7, 112.2, 111.7, 82.7, 66.2, 56.2, 51.7, 47.1, 44.6, 38.3, 32.9, 31.6, 28.8, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 662.3305, found 662.3301.

A solution of the above *tert*-butyl ester (460 mg, 0.72 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **26** (420 mg, 100%) as a yellowish foam: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.00 (br. s, 1 H), 7.35-6.70 (m, 7H), 5.82 (m, 1 H), 5.33 (d, J = 4.5 Hz, 1 H), 4.71 (m, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.38 (d, J = 12.6 Hz, 1 H), 3.24 (td, J = 12.3, 2.7 Hz, 1 H), 2.60 (m, 2 H), 2.45-2.05 (m, 3 H), 1.70 (m, 6 H), 1.45 (m, 2 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.0, 172.0, 169.8, 167.8, 158.2, 149.4, 147.8, 142.2, 133.7, 130.2, 129.4, 128.6, 125.7, 120.6, 120.3, 115.5, 112.2, 111.8, 111.7, 108.2, 65.5, 56.3, 51.9, 47.2, 44.6, 38.5, 32.9, 31.7, 28.4, 27.0, 25.3, 23.9, 23.4, 21.8, 21.5, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 606.2679, found: 606.2692.

(1*R*)-3-(3,4,5-Trimethoxyphenyl)-1-[3-(hydroxycarbonylmethoxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (**27**)

A solution of alcohol **14** (650 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 382 mg, 1.5 mmol, followed by 1,3-dicyclohexylcarbodiimide (370 mg, 1.8 mmol), and 4-(dimethylamino)-pyridine (128 mg, 1.0 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir overnight. The mixture was then filtered through glass wool and chromatographed (silica gel, 20-30% EtOAc/hexanes) to give (1*R*)-3-(3,4,5-trimethoxyphenyl)-1-[3-(*tert*-butoxycarbonylmethoxy)phenyl]-1-

propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (776 mg, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.30-6.80 (m, 4 H), 6.37 (s, 2 H), 5.82 (t, J = 6.1 Hz, 1 H), 5.33 (d, J = 5.2 Hz, 1 H), 4.54 (s, 2 H), 3.85 (s, 6 H), 3.83 (s, 3 H), 3.38 (d, J = 12.6 Hz, 1 H), 3.16 (td, J = 12.8, 3.1 Hz, 1 H), 2.60 (m, 2 H), 2.45-2.05 (m, 3 H), 1.70 (m, 6 H), 1.50 (s, 9 H), 1.45 (m, 2 H), 1.25 (s, 3 H), 1.23 (s, 3 H), 0.90 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 175.1, 170.1, 168.2, 167.6, 158.5, 153.6, 141.7, 137.0, 130.1, 120.9, 120.2, 114.6, 113.7, 105.7, 82.7, 66.2, 61.2, 56.5, 51.7, 47.1, 44.6, 38.2, 32.9, 32.4, 28.4, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1.

A solution of the above *tert*-butyl ester (400 mg, 0.60 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **27** (358 mg, 98%) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.30-6.80 (m, 4 H), 6.39 (s, 2 H), 5.82 (m, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.70 (m, 2 H), 3.86 (s, 6 H), 3.84 (s, 3 H), 3.38 (d, J = 12.6 Hz, 1 H), 3.22 (td, J = 12.8, 3.1 Hz, 1 H), 2.60 (m, 2 H), 2.45-2.05 (m, 3 H), 1.70 (m, 6 H), 1.45 (m, 2 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.0, 175.0, 171.7, 169.8, 167.8, 158.2, 153.6, 142.1, 136.9, 130.2, 129.4, 128.6, 125.7, 120.3, 115.5, 111.8, 107.9, 105.8, 65.6, 61.2, 56.5, 52.0, 47.2, 44.6, 38.3, 32.9, 32.5, 27.0, 25.3, 23.8, 23.4, 21.5, 9.1. MS(FAB): $(M+Na)^+$ calcd: 636.2785, found: 636.2756.

(R) 1-(3-(Hydroxycarbonylmethoxy)phenyl)-3-(3,4-methylendioxyphenyl)-1-propyl (2S)-1-(3,3'-dimethyl-1,2-dioxopentyl)-2-piperdinecarboxylate (**28**)

A solution of (R) 1-(3-(*tert*-Butoxycarbonylmethoxy)phenyl)-3-(3,4-methylenedioxyphenyl) propan-1-ol (**15**) (500 mg, 1.29 mmol) in CH_2Cl_2 (4 mL) at 0 °C was treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 330 mg, 1.29 mmol, prepared from L-pipecolic acid in 4 steps following literature procedures by Holt et al. *J. Amer. Chem. Soc.*, **1993**, *115*, 9925-9938) followed by 4-(dimethylamino)pyridine (DMAP 1 mg) and 1,3-dicyclohexyl carbodiimide (DCC, 267 mg, 1.29 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir for 2 h then diluted with diethyl ether (20 mL). The reaction mixture was filtered, evaporated, and flash chromatographed . Flash chromatography (silica gel, 20% → 30%% EtOAc/hexanes) of crude material afforded 556 mg (69%) of a clear colorless oil: IR (neat) 2970, 1745, 1700, 1640, 1490, 1440, 1245, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.32-7.26 (m, 1H), 6.99-6.84 (m, 6H), 5.93 (s, 2H). 5.80-76 (m, 1H), 5.33 (d, J = 4.9 Hz, 1H), 4.55 (s, 2H), 3.38 (br d, J = 12.9 Hz, 1H), 3.16 (td, J = 12.3, 3.1 Hz, 1H), 2.63-2.50 (m, 2H), 2.38 (br d, J = 13.7 Hz,

1H), 2.26-2.16 (m, 1H), 2.09-2.04 (m, 1H), 1.81-1.57 (m, 7H), 1.51 (s, 9H), 1.26, (s, 3H), 1.23 (s, 3H), 0.91(t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.3, 167.6, 158.5, 148.1, 146.2, 141.7, 135.0, 130.1, 121.5, 120.2, 114.9, 113.6, 109.2, 108.6, 101.2, 82.7, 66.2, 51.7, 47.1, 44.5, 38.3, 32.9, 31.6, 28.4, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 646.2992, found 646.3021.

A solution of the above *tert*-butyl ester (625 mg, 1.00 mmol) in CH_2Cl_2 (4.0 mL) was treated with trifluoroacetic acid (1.5 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **28** (483 mg, 85%) as a clear colorless oil: IR (neat) 3420, 2940, 1735, 1700, 1640, 1490, 1440, 1245, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.12 (t, J = 6.7 Hz, 1H), 6.92-6.81 (m, 3H), 6.68-6.52 (m, 3H), 5.86 (s, 2H), 5.73 (t, J = 7.2 Hz, 1H), 5.33 (s, 1H), 4.40 (s, 2H), 3.34 (d, J = 12.2 Hz, 1H), 3.19 (t, J = 12.0 Hz, 1H), 2.54-2.46 (m, 2H), 2.34 (d, J = 12.6 Hz, 1H), 2.24-2.00 (m, 2H), 1.73- 1.32 (m, 7H), 1.18 (s, 3H), 1.16 (s, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) (single diastereomer, mixture of rotamers) 208.0, 169.9, 167.79, 158.3, 148.0, 146.2, 141.9, 135.0, 130.1, 121.5, 109.1, 108.6, 107.2, 101.2, 77.0, 51.9, 47.0, 44.6, 38.6, 32.9, 31.8, 26.9, 25.3, 23.9, 23.3, 21.6, 9.1.

(1*R*)-3-(3-Pyridyl)-1-(3-(hydroxycarbonylmethoxy)phenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (**29**)

A solution of alcohol **21** (530 mg, 1.54 mmol) in CH_2Cl_2 (5 mL) was treated with (2*S*)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylic acid (**23**, 393 mg, 1.54 mmol, followed by 1,3-dicyclohexylcarbodiimide (381 mg, 1.85 mmol), and 4-(dimethylamino)-pyridine (132 mg, 1.08 mmol) under a nitrogen atmosphere. The resulting bright yellow suspension was allowed to stir overnight. The mixture was then filtered through glass wool and chromatographed (silica gel, 20-60% EtOAc/hexanes) to give (1*R*)-3-(3-Pyridyl)-1-[3-(*tert*-butoxycarbonylmethoxy)phenyl]-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (860 mg, 96%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.46 (m, 2 H), 7.50-6.80 (m, 6 H), 5.80 (t, J = 6.1 Hz, 1 H), 5.32 (d, J = 5.0 Hz, 1 H), 4.54 (s, 2 H), 3.38 (d, J = 12.8 Hz, 1 H), 3.14 (td, J = 12.6, 3.0 Hz, 1 H) 2.60 (m, 2 H), 2.36 (d, J = 13.7 Hz, 1 H), 2.25 (m, 1 H), 2.10 (m, 1 H), 1.75 (m, 4 H), 1.49 (s, 9 H), 1.45 (m, 2 H), 1.24 (s, 3 H), 1.22 (s, 3 H), 0.90 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 175.1, 170.0, 168.2, 167.7, 158.6, 150.2, 148.1, 141.3, 136.6, 130.2, 123.8, 120.1, 115.0, 113.6, 107.9, 82.8, 66.1, 51.7, 47.1, 44.6, 39.2, 37.8, 34.4, 33.0, 29.2, 28.4, 26.7, 25.3, 23.9, 23.5, 21.6, 21.4, 9.1.

A solution of the above *tert*-butyl ester (400 mg, 0.69 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **29** (424 mg, 96%, trifluoroacetic acid salt) as a white foam: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.75 (s, 1 H), 8.67 (d, J = 10.4 Hz, 1 H), 8.23 (t, J = 5.6 Hz, 1 H), 7.79 (dd, J = 7.9, 5.6 Hz, 1 H), 7.35-6.75 (m, 4 H), 5.80 (t, J = 6.1 Hz, 1 H), 5.25 (d, J = 5.0 Hz, 1 H), 4.75 (m, 2 H), 3.35 (d, J = 13.2 Hz, 1 H), 3.14 (td, J = 12.6, 3.0 Hz, 1 H) 2.75 (m, 2 H), 2.30 (m, 3 H), 1.70 (m, 6 H), 1.40 (m, 2 H), 1.22 (s, 6 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 172.3, 169.9, 167.8, 158.6, 145.5, 142.5, 142.0, 139.8, 139.5, 130.6, 129.4, 128.6, 120.2, 117.1, 111.8, 65.2, 51.8, 47.1, 44.8, 36.7, 32.8, 28.4, 26.6, 25.2, 23.7, 21.4, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 547.2420, found: 547.2415.

(1*R*)-3-(3-Indolyl)-1-(3-(hydroxycarbonylmethoxy)phenyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarboxylate (**30**)

The *tert*-butyl ester was prepared in a similar manner as the ester of **28** from (R) 1-(3-(*tert*-Butoxycarbonylmethoxy) phenyl)-3-(3-indoyl)propan-1-ol (**22**). Flash chromatography (silica gel, 30% EtOAc/hexanes) afforded 492 mg (76%) of clear colorless oil: IR (neat) 3410, 2970, 1735, 1700, 1635, 1455, 1225, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 8.04 (br s, 1H), 7.53 (d, J = 7.8 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1H), 7.30-7.11 (m, 3H), 7.01-6.84 (m, 4H), 5.91-5.86 (m, 1H), 5.35 (d, J = 4.8 Hz, 1H), 4.54 (s, 2H), 3.39 (d, J = 13.3 Hz, 1H), 3.18 (td, J = 12.6, 3.0 Hz, 1H), 2.87-2.74 (m, 2H), 2.41-2.18 (m, 3H), 1.82-1.57 (m, 7H), 1.50 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 208.3, 170.1, 168.3, 167.7, 158.5, 141.9, 136.8, 130.1, 127.7, 122.3, 121.8, 120.3, 119.6, 119.1, 115.4, 114.7, 113.7, 111.5, 82.7, 66.2, 51.7, 47.1, 44.5, 36.8, 32.9, 28.4, 26.9, 25.4, 24.0, 23.4, 21.6, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 641.3203, found: 641.3193.

A solution of the above *tert*-butyl ester (112 mg, 0.18 mmol) in CH_2Cl_2 (5.0 mL) was treated with trifluoroacetic acid (1.0 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **30** (102 mg, 100%) as a brown foam: ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.90-6.70 (m, 10 H), 5.85 (m, 1 H), 5.35 (m, 1 H), 4.62 (m, 2 H), 3.40 (m, 1 H), 3.25 (m, 1 H), 2.80 (m, 2 H), 2.40-2.05 (m, 3 H), 1.85-1.45 (m, 12 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.0, 175.0, 169.8, 167.9, 158.2, 142.3, 130.2, 129.4, 128.6, 125.7, 122.5, 119.7, 119.1, 115.3, 111.6, 108.0, 65.5, 52.0, 47.2, 44.6, 32.9, 27.0, 25.3, 23.9, 23.4, 21.6, 9.1. HRMS(FAB): $(M+Na)^+$ calcd: 585.2577, found: 585.2561.

Preparation of Dimerizers

Example 1. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] 1,4-phenylenediacetamide (31)

A mixture of 1,4-phenylenediacetic acid (194 mg, 1.0 mmol) and disuccinimidyl carbonate (512 mg, 2.0 mg) in anhydrous acetonitrile (5.0 mL) was treated with pyridine (243 μL, 3.0 mmol). The mixture was stirred at room temperature under nitrogen overnight. The resulting suspension was partitioned between EtOAc (70 mL) and water (50 mL). The organic layer was separated, washed with 1 M Na_2CO_3, water, 0.5 N HCl, saturated brine, dried (Na_2SO_4), and concentrated *in vacuo* to give disuccinimidyl 1,4-phenylenediacetate (144 mg, 37%) as a white solid. ^1H NMR (DMSO-d_6, 300 MHz) 7.34 (s, 4 H), 4.10 (s, 4 H), 2.80 (s, 8 H).

A solution of **24** (102 mg, 0.16 mmol) in CH_2Cl_2 (2.0 mL) was treated with the above activated diester (31 mg, 0.080 mmol) and Et_3N (67 μL, 0.48 mmol). The mixture was stirred at room temperature overnight. The resulting clear solution was impregnated on silica gel and evaporated to dryness. Chromatography (silica gel, 50 - 100% EtOAc/hexanes) provided **31** (60 mg, 62%) as a white solid: mp 55-57 °C; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.32-7.15 (m, 16 H), 6.95 (d, J = 7.7 Hz, 2 H), 6.83 (s, 2 H), 6.74 (m, 2 H), 6.01 (br. s, 2 H), 5.80 (t, J = 5.8 Hz, 2 H), 5.32 (d, J = 4.9 Hz, 2 H), 3.98 (t, J = 5.7 Hz, 4 H), 3.52 (s, 4 H), 3.50-3.30 (m, 6 H), 3.22 (td, J = 12.4, 2.6 Hz, 2 H), 2.67 (m, 4 H), 2.38 (d, J = 13.6 Hz, 2 H), 2.30 (m, 2 H), 2.12 (m, 2 H), 1.95 (t, J = 6.1 Hz, 4 H), 1.85-1.60 (m, 10 H), 1.50 (m, 4 H), 1.23 (s, 6 H), 1.21 (s, 6 H), 0.89 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 208.0, 171.3, 170.1, 169.9, 167.8, 159.2, 141.8, 141.6, 141.2, 134.4, 130.3, 130.1, 128.9, 128.7, 126.5, 119.3, 115.0, 114.7, 113.1, 112.8, 57.1, 51.7, 47.1, 44.5, 43.7, 39.3, 38.3, 38.2, 37.8, 33.0, 32.8, 32.1, 29.3, 26.9, 25.3, 23.9, 23.5, 21.6, 21.4, 9.17,.9.13. MS(FAB): $(M+Na)^+$ 1225, $(M+H)^+$ 1203.

Example 2. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] suberamide (32)

Following the same procedure as in Example 1 except replacing suberic acid for 1,4-phenylenediacetic acid, obtained **32** (54 mg, 56%) as a white solid. mp 44-46 °C; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.85 (m, 18 H), 6.18 (br. s, 2 H), 5.86 (t, J = 5.9 Hz, 2 H), 5.39 (d, J = 4.9 Hz, 2 H), 4.12 (t, J = 5.9 Hz, 4 H), 3.60-3.40 (m, 6 H), 3.28 (td, J = 12.6, 2.8 Hz, 2 H), 2.70 (m, 4 H), 2.47 (d, J = 13.8 Hz, 2 H), 2.35 (m, 2 H), 2.30-2.00 (m, 12 H), 1.95-1.70 (m, 14 H), 1.55-1.35 (m, 6 H),

1.30 (s, 6 H), 1.28 (s, 6 H), 0.96 (t, J = 7.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 170.0, 167.8, 159.3, 141.8, 141.2, 130.2, 128.9, 128.7, 126.5, 119.4, 114.7, 113.0, 66.4, 51.7, 47.1, 44.5, 38.3, 37.7, 32.8, 32.1, 29.3, 28.7, 26.9, 25.8, 25.3, 23.9, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1205.

Example 3. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] pyridine-2,6-dicarboxamide (33)

Following the same procedure as in Example 1 except replacing pyridine-2,6-dicarboxylic acid for 1,4-phenylenediacetic acid, obtained **33** (44 mg, 54%) as a white solid. mp 60-62 °C; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.34 (d, J = 7.7 Hz, 2 H), 8.00 (t, J = 7.7 Hz, 1 H), 7.99 (br. s, 2 H, NHs), 7.30-6.75 (m, 18 H), 5.77 (t, J = 5.7 Hz, 2 H), 5.30 (d, J = 4.8 Hz, 2 H), 4.02 (m, 4 H), 3.63 (m, 4 H), 3.35 (d, J = 12.7 Hz, 2 H), 3.20 (td, J = 12.7, 2.8 Hz, 2 H), 2.60 (m, 4 H), 2.36 (d, J = 13.3 Hz, 2 H), 2.24 (m, 2 H), 2.05 (m, 6 H), 1.80-1.65 (m, 10 H), 1.50 (m, 4 H), 1.20 (s, 6 H), 1.18 (s, 6 H), 0.85 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.1, 167.7, 164.0, 159.3, 149.1, 142.0, 141.2, 139.3, 130.2, 128.9, 128.7, 126.5, 125.4, 119.4, 115.1, 113.2, 107.9, 67.0, 57.1, 51.6, 47.1, 44.5, 38.3, 37.9, 32.8, 32.1, 29.6, 28.0, 26.9, 25.4, 23.9, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1198, $(M+H)^+$ 1176.

Example 4. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] pyridine-3,5-dicarboxamide (34)

Following the same procedure as in Example 1 except replacing pyridine-3,5-dicarboxylic acid for 1,4-phenylenediacetic acid, obtained **34** (32 mg, 39%) as a white solid. mp 62-64 °C; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 9.09 (d, J = 1.8 Hz, 2 H), 8.42 (d, J = 1.9 Hz, 1 H), 7.30-6.80 (m, 20 H), 5.78 (t, J = 5.6 Hz, 2 H), 5.28 (d, J = 4.7 Hz, 2 H), 4.12 (t, J = 5.6 Hz, 4 H), 3.68 (m, 4 H), 3.36 (d, J = 13.0 Hz, 2 H), 3.18 (td, J = 13.4, 3.4 Hz, 2 H), 2.60 (m, 4 H), 2.35 (d, J = 13.2 Hz, 2 H), 2.25 (m, 2 H), 2.05 (m, 6 H), 1.80-1.65 (m, 10 H), 1.50 (m, 4 H), 1.18 (s, 6 H), 1.16 (s, 6 H), 0.84 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 170.1, 167.8, 165.2, 159.1, 150.9, 141.9, 141.3, 130.3, 130.2, 128.9, 128.7, 126.5, 119.5, 115.0, 112.7, 107.9, 67.0, 51.7, 47.1, 44.5, 38.7, 38.2, 32.8, 32.1, 26.8, 25.3, 23.9, 23.5, 21.5, 9.1. MS(FAB): $(M+Na)^+$ 1198, $(M+H)^+$ 1176.

Example 5. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] N-methyl-pyridinium-3,5-dicarboxamide iodide (35)

A solution of **34** (10 mg, 8.5 μmol) in acetone (1.0 mL) was treated with MeI (60 μL, 10.2 mmol). The mixture was left to stand at room temperature under dark for 3 d and TLC (100% EtOAc) showed all starting material converted to a baseline compound. The resulting deep yellow solution was concentrated *in vacuo* to afford **35** (11 mg, 100%) as a yellow solid. ^{1}H NMR (Acetone-d$_6$, 300 MHz) (single diastereomer, mixture of rotamers) 9.98 (s, 1 H), 9.62 (s, 2 H), 9.14 (br. s, 2 H), 7.20-6.70 (m, 20 H), 5.83 (t, J = 5.2 Hz, 2 H), 5.27 (d, J = 4.5 Hz, 2 H), 4.75 (s, 3 H), 4.18 (t, J = 6.4 Hz, 4 H), 3.67 (q, J = 6.1 Hz, 4 H), 3.45 (d, J = 13.4 Hz, 2 H), 3.25 (m, 2 H), 2.75 (m, 4 H), 2.20-1.90 (m, 10 H), 1.75 (m, 10 H), 1.50 (m, 4 H), 1.21 (s, 6 H), 1.19 (s, 6 H), 0.85 (t, J = 7.5 Hz, 6 H); ^{13}C NMR (Acetone-d$_6$, 75MHz) (single diastereomer, mixture of rotamers) 208.7, 170.8, 168.2, 162.1, 160.6, 148.7, 143.3, 142.6, 130.8, 129.6, 127.2, 119.8, 115.6, 113.9, 104.0, 77.8, 67.2, 52.5, 47.6, 45.3, 39.4, 38.1, 33.6, 32.8, 27.6, 26.1, 24.2, 23.8, 22.4, 9.5. MS(FAB): M$^+$ 1190.

Example 6. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] benzene-1,3-disulfonamide (36)

A solution of **24** (106 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL) was treated with Et_3N (71 μL, 0.51 mmol) and benzene-1,3-disulfonyl chloride (23 mg, 0.085 mmol). The mixture was stirred at room temperature overnight. The resulting yellow solution was then impregnated on silica gel and evaporated to dryness. Chromatography (silica gel, 50% EtOAc/hexanes) afforded **36** (64 mg, 61%) as a white solid. mp 58-60 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.39 (d, J = 6.3 Hz, 1 H), 8.03 (dd, J = 7.8, 1.6 Hz, 2 H), 7.57 (td, J = 7.9, 4.4 Hz, 1 H), 7.35-6.80 (m, 18 H), 5.81 (m, 2 H), 5.50 (m, 2 H), 5.36 (d, J = 4.4 Hz, 2 H), 3.95 (m, 4 H), 3.43 (d, J = 12.6 Hz, 2 H), 3.22 (m, 6 H), 2.65 (m, 4 H), 2.43 (d, J = 13.6 Hz, 2 H), 2.30 (m, 2 H), 2.15 (m, 2 H), 1.95 (m, 4 H), 1.90-1.65 (m, 12 H), 1.50 (m, 4 H), 1.25 (s, 6 H), 1.23 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.5, 170.1, 167.8, 159.0, 142.1, 141.9, 141.3, 131.1, 130.5, 130.1, 128.9, 128.7, 126.5, 125.8, 119.5, 114.8, 112.7, 65.7, 57.2, 51.8, 47.1, 44.6, 41.2, 38.4, 32.9, 32.8, 32.1, 29.5, 26.8, 25.3, 23.9, 23.4, 21.6, 9.2, 9.1. MS(FAB): (M+Na)$^+$ 1269.

Example 7. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] 5-aminobenzene-1,3-dicarboxamide (37)

A mixture of 5-aminoisophthalic acid (1.81 g, 10 mmol) and dioxane (60 mL) was treated with a solution of Na_2CO_3 (4.24 g, 40 mmol) in water (60 mL) and then with $(Boc)_2O$ (3.5 mL, 15 mmol). The mixture was stirred at room temperature for 16 h. EtOAc (100 mL) was added to the mixture and 10% $KHSO_4$ (*ca.* 100 mL) added to bring the pH to 2. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined EtOAc solution was washed with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo* to give 5-*tert*-butyloxycarbamyl-benzene-1,3-dicarboxylic acid (2.8 g, 100%).

A mixture of the above diacid (422 mg, 1.5 mmol) and disuccinimidyl carbonate (768 mg, 3.0 mmol) in acetonitrile (20 mL) was treated with pyridine (364 µL, 4.5 mmol). The mixture was stirred vigorously at room temperature for 20 h. The resulting suspension was partitioned between EtOAc (150 mL) and 0.5 N HCl (50 mL). The organic layer was separated and then washed with water (50 mL), 10% $NaHCO_3$ (2 x 50 mL), saturated brine, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (silica gel, 70%EtOAc/hexanes) afforded disuccinimidyl (5-*tert*-butyloxycarbamyl)benzene-1,3-dicarboxylate (193 mg, 27%) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) 8.50 (s, 1 H), 8.44 (s, 2 H), 6.91 (s, 1 H), 2.89 (s, 8 H), 1.54 (s, 9 H).

To a solution of **24** (81 mg, 0.127 mmol) in CH_2Cl_2 (2.0 mL) was added the above activated diester (30 mg, 0.064 mmol), followed by dropwise addition of Et_3N (53 µL, 0.38 mmol). The mixture was stirred at room temperature for 4 h. The resulting clear solution was impregnated on silica gel and evaporated to dryness. Chromatography (silica gel, 50 - 70% EtOAc/hexanes) provided *N*-Boc-**37** (56 mg, 68%) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 8.01 (s, 2 H), 7.93 (s, 1 H), 7.35-6.85 (m, 21 H), 5.83 (t, J = 6.0 Hz, 2 H), 5.34 (d, J = 4.6 Hz, 2 H), 4.14 (t, J = 5.2 Hz, 4 H), 3.70 (m, 4 H), 3.42 (d, J = 12.8 Hz, 2 H), 3.22 (t, J = 10.2 Hz, 2 H), 2.65 (m, 4 H), 2.40 (d, J = 13.0 Hz, 2 H), 2.30 (m, 2 H), 2.15 (m, 6 H), 1.85-1.65 (m, 10 H), 1.57 (s, 9 H), 1.50 (m, 4 H), 1.25 (s, 6 H), 1.23 (s, 6 H), 0.91 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.4, 170.1, 167.8, 166.8, 159.3, 153.1, 141.7, 141.3, 139.9, 136.1, 130.1, 128.8, 128.7, 126.5, 119.7, 119.4, 115.0, 112.8, 66.7, 51.7, 47.1, 44.5, 38.4, 38.2, 32.8, 32.1, 29.4, 28.7, 26.8, 25.3, 23.4, 21.5, 9.1.

A solution of *N*-Boc-**37** (20 mg, 0.016 mmol) in CH_2Cl_2 (4.0 mL) was treated with trifluoroacetic acid (0.8 mL) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **37** trifluoroacetic acid salt (20 mg, 96%) as a colorless gum. ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.67 (s, 1 H), 7.45-6.90 (m, 22 H), 5.88 (m, 2 H), 5.40 (d, J = 4.6 Hz, 2 H), 4.80 (br. s, 4 H), 4.20 (m, 4 H), 3.75 (m, 4 H), 3.45 (d, J =

12.7 Hz, 2 H), 3.32 (m, 2 H), 2.75 (m, 4 H), 2.50-2.30 (m, 4 H), 2.20 (m, 6 H), 1.78 (m, 10 H), 1.50 (m, 4 H), 1.32 (s, 6 H), 1.30 (s, 6 H), 0.98 (t, J = 7.4 Hz, 6 H). MS(FAB): $(M+H)^+$ 1190.

Example 8. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] (±)-2,6-diaminopimelamide (38)

Following the same procedures as in Example 7 except replacing (±)-2,6-diaminopimelic acid for 5-aminoisophthalic acid, obtained di-Boc-**38** (51 mg, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.50 (m, 20 H), 5.84 (t, J = 5.8 Hz, 2 H), 5.45-5.20 (m, 4 H), 4.08 (t, J = 5.4 Hz, 4 H), 3.55-3.30 (m, 6 H), 3.24 (t, J = 12.5 Hz, 2 H), 2.70 (m, 4 H), 2.42 (d, J = 13.0 Hz, 2 H), 2.35 (m, 2 H), 2.20 (m, 2 H), 2.05 (m, 4 H), 2.00-1.65 (m, 14 H), 1.50 (m, 4 H), 1.47 (s, 18 H), 1.28 (s, 6 H), 1.25 (s, 6 H), 0.94 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 170.1, 159.3, 141.8, 141.3, 130.1, 128.9, 128.7, 126.5, 119.3, 113.1, 80.4, 66.7, 51.7, 47.1, 44.5, 38.3, 32.8, 32.1, 29.5, 28.74, 28.72, 26.9, 25.3, 24.0, 23.4, 21.6, 9.1.

A solution of di-Boc-**38** (20 mg, 0.014 mmol) in CH_2Cl_2 (4.0 mL) was treated with trifluoroacetic acid (0.8 mL) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with toluene (150 mL) and concentrated *in vacuo* to give **38** di-(trifluoroacetic acid) salt (18.9 mg, 94%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.40-6.85 (m, 20 H), 5.85 (m, 2 H), 5.38 (m, 2 H), 4.05 (m, 6 H), 3.45-3.25 (m, 8 H), 2.70 (m, 4 H), 2.45 (m, 2 H), 2.40 (m, 2 H), 2.20 (m, 2 H), 2.05 (m, 4 H), 1.95-1.60 (m, 14 H), 1.50 (m, 4 H), 1.28 (s, 6 H), 1.27 (s, 6 H), 0.95 (t, J = 7.4 Hz, 6 H). MS(FAB): $(M+H)^+$ 1199.

Example 9. *N,N'-Bis*[3-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propylphenoxy)propyl] triethyleneglycol-1,10-biscarbamate (39)

To a solution of **24** (85 mg, 0.13 mmol) in CH_2Cl_2 at 0 °C was added Et_3N, followed by triethylene glycol bis(chloroformate). The mixture was stirred at 0 °C for 1 h, and TLC showed no starting material left. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica (70-80% EtOAc/hexanes) to give **39** as a colorless gum, 40 mg (48%). ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.25-6.70 (m, 18 H), 5.71 (t, J = 5.8 Hz, 2 H), 5.25 (d, J = 4.7 Hz, 2 H), 5.12 (br. s., 2 H), 4.15 (t, J = 4.4 Hz, 4 H), 3.95 (t, J = 5.9 Hz, 4 H), 3.60 (t, J = 4.8 Hz, 4 H), 3.57 (s, 4 H), 3.30 (m, 6 H), 3.10 (td, J = 12.7, 3.0 Hz, 2 H), 2.50 (m, 4 H), 2.30 (d, J = 13.7 Hz, 2 H), 2.20 (m, 2 H), 2.05 (m, 2 H), 1.92 (t, J = 6.2 Hz, 4 H), 1.75-1.50 (m, 10 H), 1.35 (m, 4H), 1.16 (s, 6 H), 1.13 (s, 6 H), 0.81 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$,

75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.1, 167.6, 159.3, 159.9, 156.9, 141.7, 141.3, 130.1, 128.9, 128.7, 126.5, 119.4, 114.8, 113.2, 71.0, 70.1, 66.0, 64.3, 51.7, 47.1, 44.5, 39.2, 38.8, 38.3, 33.0, 32.9, 32.1, 29.9, 26.8, 25.4, 23.9, 23.8, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1269.

Example 10. 1,4-Xylyldiamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propy)phenoxyacetamide] (**40**)

A solution of carboxylic acid **25** (104 mg, 0.20 mmol) in acetonitrile (2.0 mL) was treated with disuccinimidyl carbonate (56 mg, 0.22 mmol) and pyridine (48 μL, 0.60 mmol). The mixture was stirred at room temperature overnight. The mixture was then partitioned between EtOAc (70 mL) and water (50 mL). The organic phase was separated, washed with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a white foam (115 mg, 93%). The activated succinimidyl ester was redissolved in anhydrous acetonitrile (2.0 mL). The solution was then treated with triethylamine (75 μL, 0.54 mmol) followed by a solution of 1,4-xylyldiamine in DMF (0.32 M, 288 μL, 0.092 mmol). The resulting suspension was stirred at room temperature for 1 h and TLC showed no starting material left. The mixture was partitioned between EtOAc (50 mL) and water (20 mL). The organic layer was separated, washed with 0.5 N HCl (aq.), saturated brine, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (silica gel, 70% EtOAc/hexanes) afforded **40** (42 mg, 40%) as a white solid: mp 59-61 °C; ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.25-6.70 (m, 22 H), 5.69 (m, 2 H), 5.22 (d, J = 4.8 Hz, 2 H), 4.46 (s, 4 H), 4.43 (d, J = 3.9 Hz, 4 H), 3.27 (d, J = 13.2 Hz, 2 H), 3.06 (td, J = 12.6, 2.6 Hz, 2 H), 2.50 (m, 4 H), 2.27 (d, J = 13.4 Hz, 2 H), 2.16 (m, 2 H), 2.00 (m, 2 H), 1.75-1.50 (m, 10 H), 1.35 (m, 4 H), 1.12 (s, 6 H), 1.10 (s, 6 H), 0.78 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.3, 170.0, 168.4, 168.3, 167.6, 157.7, 142.2, 142.1, 141.1, 137.6, 130.4, 128.9, 128.7, 128.5, 126.6, 120.6, 114.3, 113.8, 67.7, 57.0, 51.6, 47.1, 44.5, 43.0, 39.2, 38.4, 38.1, 32.9, 32.1, 32.0, 26.8, 25.3, 23.9, 23.5, 21.6, 9.2. MS(FAB): $(M+Na)^+$ 1169, $(M+H)^+$ 1147.

Example 11. 1,4-*Bis*(3-aminopropyl)piperazine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propyl)phenoxyacetamide] (**41**)

Following the same method as in Example 10 except replacing 1,4-bis(3-aminopropyl)piperazine for 1,4-xylyldiamine, obtained **41** (35 mg, 53%) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.55-6.90 (m, 20 H), 5.93 (t, J = 5.6 Hz, 2 H), 5.46 (d, J = 4.8 Hz, 2 H), 4.63 (s, 4 H), 3.70-3.50 (m, 6 H),

3.37 (m, 2 H), 2.95 -2.20 (m, 24 H), 1.90 (m, 16 H), 1.60 (m, 4 H), 1.37 (s, 6 H), 1.35 (s, 6 H), 1.03 (t, J = 7.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.4, 167.7, 158.0, 142.3, 141.1, 130.4, 128.9, 128.7, 126.6, 120.5, 115.0, 113.8, 107.9, 68.2, 51.6, 47.1, 44.5, 38.5, 32.9, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1. MS(FAB): $(M+H)^+$ 1211.

Example 12. 3,3'-Diamino-*N*-methyldipropylamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propy)phenoxyacetamide] (42)

Following the same method as in Example 10 except replacing 3,3'-Diamino-*N*-methyldipropylamine for 1,4-xylyldiamine, obtained **42** (28 mg, 48%) as a colorless gum. ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.50-6.75 (m, 20 H), 5.76 (t, J = 5.8 Hz, 2 H), 5.29 (d, J = 4.8 Hz, 2 H), 4.45 (s, 4 H), 3.35 (m, 6 H), 3.17 (td, J = 12.6, 2.7 Hz, 2 H), 2.60 (m, 4 H), 2.35 (m, 6 H), 2.25 (m, 2 H), 2.05 (m, 5 H), 1.70 (m, 14 H), 1.40 (m, 4 H), 1.20 (s, 6 H), 1.18 (s, 6 H), 0.86 (t, J = 7.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.4, 167.7, 158.0, 142.2, 141.1, 130.4, 128.9, 128.7, 126.5, 120.3, 115.0, 114.6, 113.7, 108.0, 67.9, 56.4, 51.6, 47.1, 44.5, 38.4, 33.0, 32.9, 32.1, 26.8, 25.3, 23.9, 23.5, 21.6, 21.4, 9.1. MS(FAB): $(M+H)^+$ 1156, $(M+Na)^+$ 1178.

Example 13. 1,5-Diaminopentane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propyl)phenoxyacetamide] (43)

Following the same method as in Example 10 except replacing 1,5-diaminopentane for 1,4-xylyldiamine, obtained **43** (18 mg, 30%) as a colorless gum. ^1H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.40-7.00 (m, 18 H), 6.80 (br. s., NHs, 2 H), 5.85 (m, 2 H), 5.33 (d, J = 4.7 Hz, 2 H), 4.50 (s, 4 H), 3.37 (m, 6 H), 3.20 (td, J = 12.7, 2.7 Hz, 2 H), 2.65 (m, 4 H), 2.38 (d, J = 13.4 Hz, 2 H), 2.28 (m, 2 H), 2.14 (m, 2 H), 1.90-1.40 (m, 20 H), 1.24 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.3, 167.7, 157.8, 142.2, 141.2, 130.4, 128.9, 128.7, 126.5, 120.5, 114.2, 113.9, 67.8, 51.6, 47.1, 44.5, 39.2, 38.4, 32.9, 32.0, 29.6, 26.8, 25.4, 24.4, 23.9, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1135.

Example 14. 1,5-Diamino-3-oxapetane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propyl)phenoxyacetamide] (48)

Following the same method as in Example 10 except replacing 1,5-diamino-3-oxapentane dihydrochloride (Aldrich) for 1,4-xylyldiamine, obtained 48 (23 mg, 39%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.30-6.80 (m, 20 H), 5.80 (m, 2 H), 5.30 (d, J = 4.9 Hz, 2 H), 4.48 (s, 4 H), 3.50 (br. s, 8 H), 3.36 (d, J = 13.6 Hz, 2 H), 3.16 (td, J = 12.6, 2.7 Hz, 2 H), 2.60 (m, 4 H), 2.36 (d, J = 13.8 Hz, 2 H), 2.26 (m, 2 H), 2.10 (m, 2 H), 1.80-1.60 (m, 10 H), 1.50 (m, 4 H), 1.20 (s, 6 H), 1.19 (s, 6 H), 0.87 (t, J = 7.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.5, 167.7, 157.8, 142.2, 141.1, 130.4, 128.9, 128.7, 126.5, 120.5, 114.6, 113.7, 108.1, 69.9, 67.8, 51.6, 47.1, 44.5, 39.1, 38.4, 32.9, 32.0, 26.8, 25.3, 23.9, 23.5, 21.6, 21.4, 9.1. MS(FAB): $(M+Na)^+$ 1137.

Example 15. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propyl)phenoxyacetamide] (53)

Following the same method as in Example 10 except replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine, obtained 53 (23 mg, 32%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.85 (m, 20 H), 5.80 (t, J = 5.7 Hz, 2 H), 5.33 (d, J = 4.9 Hz, 2 H), 4.51 (s, 4 H), 3.60 (br. s, 12 H), 3.40 (d, J = 12.3 Hz, 2 H), 3.20 (td, J = 12.6, 2.8 Hz, 2 H), 2.65 (m, 4 H), 2.40 (d, J = 13.4 Hz, 2 H), 2.26 (m, 2 H), 2.10 (m, 2 H), 1.90-1.60 (m, 10 H), 1.50 (m, 4 H), 1.25 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.4, 167.7, 157.8, 142.2, 141.1, 130.4, 128.9, 128.7, 126.5, 120.5, 114.7, 113.6, 70.7, 70.1, 67.8, 51.6, 47.1, 44.5, 39.2, 38.4, 32.9, 32.0, 26.8, 25.3, 23.9, 23.5, 21.6, 21.4, 9.1. MS(FAB): $(M+Na)^+$ 1181.

Example 16. 1,11-Diamino-3,6,9-trioxaundecane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-phenyl)propyl)phenoxyacetamide] (59)

Following the same method as in Example 10 except replacing 1,11-Diamino-3,6,9-trioxaundecane (prepared using literature procedure of Dietrich, B.; Lehn, J.-M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron*, 1973, *29*, 1628) for 1,4-xylyldiamine, obtained 59 (18 mg, 24%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.80 (m, 20 H), 5.77 (t, J = 6.0 Hz, 2 H), 5.30 (d, J = 4.9 Hz, 2 H), 4.48 (s, 4 H), 3.60 (m, 16 H), 3.35 (d, J = 13.5 Hz, 2 H), 3.16 (td, J = 12.6, 2.9 Hz, 2 H), 2.65 (m, 4 H), 2.37 (d, J = 13.6 Hz, 2 H), 2.25 (m, 2 H), 2.05 (m, 2 H), 1.80-1.60 (m,

12 H), 1.50 (m, 4 H), 1.21 (s, 6 H), 1.19 (s, 6 H), 0.87 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.4, 167.7, 157.8, 142.2, 141.1, 130.4, 128.9, 128.7, 126.5, 120.5, 114.7, 113.6, 108.0, 70.9, 70.7, 70.1, 67.8, 51.6, 47.1, 44.5, 39.2, 38.4, 32.9, 32.0, 26.8, 25.3, 23.9, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1125.

Example 17. 1,5-Diaminopentane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (**44**)

Following the same method as in Example 10 except replacing the acid monomer **26** for **25** and replacing 1,5-diaminopentane for 1,4-xylyldiamine, obtained **44** (58 mg, 49%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.65 (m, 16 H), 5.79 (m, 2 H), 5.33 (d, J = 4.8 Hz, 2 H), 4.49 (s, 4 H), 3.87 (s, 6 H), 3.86 (s, 6 H), 3.35 (m, 6 H), 3.20 (m, 2 H), 2.95 (m, 2 H), 2.60 (m, 4 H), 2.38 (d, J = 13.4 Hz, 2 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.90-1.40 (m, 20 H), 1.23 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.3, 168.2, 167.7, 157.8, 149.3, 147.8, 142.3, 133.8, 130.4, 120.6, 114.2, 113.9, 112.2, 111.8, 108.0, 67.8, 56.3, 56.2, 51.6, 47.1, 44.5, 39.2, 38.6, 38.3, 32.9, 31.6, 29.6, 26.8, 25.3, 24.4, 23.8, 23.6, 9.1. MS(FAB): $(M+Na)^+$ 1255.

Example 18. 1,5-Diamino-3-oxapetane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (**49**)

Following the same method as in Example 10 except replacing the acid monomer **26** for **25** and replacing 1,5-diamino-3-oxapentane dihydrochloride (Aldrich) for 1,4-xylyldiamine, obtained **49** (73 mg, 62%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.65 (m, 16 H), 5.79 (m, 2 H), 5.33 (d, J = 4.8 Hz, 2 H), 4.51 (s, 4 H), 3.87 (s, 6 H), 3.86 (s, 6 H), 3.55 (br.s, 8 H), 3.35 (m, 2 H), 3.20 (m, 2 H), 2.60 (m, 4 H), 2.38 (d, J = 13.4 Hz, 2 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.90-1.40 (m, 20 H), 1.23 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.0, 168.5, 168.4, 167.7, 157.8, 149.3, 147.8, 142.3, 133.7, 130.4, 120.5, 114.6, 113.7, 112.2, 111.8, 69.9, 67.8, 56.3, 56.2, 51.6, 47.1, 44.5, 39.1, 38.6, 32.9, 31.6, 26.8, 25.3, 23.8, 23.6, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1257.

Example 19. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxo-pentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (**54**)

Following the same method as in Example 10 except replacing the acid monomer **26** for **25** and replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine, obtained **54** (54 mg, 49%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.65 (m, 16 H), 5.79 (m, 2 H), 5.33 (d, J = 4.8 Hz, 2 H), 4.50 (s, 4 H), 3.87 (s, 6 H), 3.86 (s, 6 H), 3.59 (br.s, 12 H), 3.35 (m, 2 H), 3.20 (m, 2 H), 2.60 (m, 4 H), 2.38 (d, J = 13.4 Hz, 2 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.90-1.40 (m, 20 H), 1.23 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.1, 168.4, 167.7, 157.8, 149.3, 147.8, 142.3, 133.7, 130.4, 120.5, 114.7, 113.6, 112.2, 111.8, 70.6, 70.1, 67.8, 56.3, 56.2, 51.6, 47.1, 44.5, 39.2, 38.6, 32.9, 31.6, 26.8, 25.3, 23.8, 23.6, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1301.

Example 20. 1,11-Diamino-3,6,9-trioxaundecane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxo-pentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (**60**)

Following the same method as in Example 10 except replacing the acid monomer **26** for **25** and replacing 1,11-Diamino-3,6,9-trioxaundecane (prepared using literature procedure of Dietrich, B.; Lehn, J.-M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron*, **1973**, *29*, 1628) for 1,4-xylyldiamine, obtained **60** (64 mg, 50%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) (single diastereomer, mixture of rotamers) 7.35-6.65 (m, 16 H), 5.79 (m, 2 H), 5.33 (d, J = 4.8 Hz, 2 H), 4.50 (s, 4 H), 3.87 (s, 6 H), 3.86 (s, 6 H), 3.61 (m, 16 H), 3.38 (m, 2 H), 3.20 (m, 2 H), 2.60 (m, 4 H), 2.38 (m, 2 H), 2.28 (m, 2 H), 2.10 (m, 2 H), 1.90-1.40 (m, 20 H), 1.23 (s, 6 H), 1.22 (s, 6 H), 0.90 (t, J = 7.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75MHz) (single diastereomer, mixture of rotamers) 208.2, 170.1, 168.4, 167.7, 157.8, 149.3, 147.8, 142.3, 133.7, 130.4, 120.5, 114.7, 113.6, 112.2, 111.8, 108.0, 70.6, 70.1, 67.8, 56.3, 56.2, 51.6, 47.1, 44.5, 39.2, 38.6, 32.9, 31.6, 26.8, 25.3, 23.8, 23.5, 21.6, 9.1. MS(FAB): $(M+Na)^+$ 1345.

Example 21. 1,5-Diaminopentane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4,5-trimethoxyphenyl))propyl)phenoxy-acetamide] (**45**)

Following the same method as in Example 10 except replacing the acid monomer **27** for **25** and replacing 1,5-diaminopentane for 1,4-xylyldiamine, obtained **45** (33 mg,

34%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1315.

Example 22. 1,5-Diamino-3-oxapetane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4,5-trimethoxyphenyl))propyl)phenoxy-acetamide] (**50**)

Following the same method as in Example 10 except replacing the acid monomer **27** for **25** and replacing 1,5-diamino-3-oxapentane dihydrochloride (Aldrich) for 1,4-xylyldiamine, obtained **50** (41 mg, 46%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1317.

Example 23. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4,5-trimethoxyphenyl))propyl)phenoxy-acetamide] (**55**)

Following the same method as in Example 10 except replacing the acid monomer **27** for **25** and replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine for 1,4-xylyldiamine, obtained **55** (37 mg, 38%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1361.

Example 24. 1,11-Diamino-3,6,9-trioxaundecane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4,5-trimethoxyphenyl))propyl)phenoxy-acetamide] (**61**)

Following the same method as in Example 10 except replacing the acid monomer **27** for **25** and replacing 1,11-Diamino-3,6,9-trioxaundecane for 1,4-xylyldiamine, obtained **61** (27 mg, 32%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1405.

Example 25. 1,5-Diaminopentane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-methylenedioxyphenyl))propyl)phenoxy-acetamide] (**46**)

Following the same method as in Example 10 except replacing the acid monomer **28** for **25** and replacing 1,5-diaminopentane for 1,4-xylyldiamine, obtained **46** (42 mg, 42%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1223.

Example 26. ,5-Diamino-3-oxapetane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-methylenedioxyphenyl))propyl)phenoxy-acetamide] (**51**)

Following the same method as in Example 10 except replacing the acid monomer **28** for **25** and replacing 1,5-diamino-3-oxapentane dihydrochloride (Aldrich) for 1,4-xylyldiamine, obtained **51** (39 mg, 34%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1225.

Example 27. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-methylenedioxyphenyl))propyl)phenoxy-acetamide] (**56**)

Following the same method as in Example 10 except replacing the acid monomer **28** for **25** and replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine for 1,4-xylyldiamine, obtained **56** (55 mg, 47%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1269.

Example 28. 1,11-Diamino-3,6,9-trioxaundecane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-methylenedioxyphenyl))propyl)phenoxy-acetamide] (**62**)

Following the same method as in Example 10 except replacing the acid monomer **28** for **25** and replacing 1,11-Diamino-3,6,9-trioxaundecane for 1,4-xylyldiamine, obtained **62** (52 mg, 42%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1313.

Example 29. 1,5-Diaminopentane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (**47**)

Following the same method as in Example 10 except replacing the acid monomer **29** for **25** and replacing 1,5-diaminopentane for 1,4-xylyldiamine, obtained **47** (64 mg, 58%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1137.

Example 30. 1,5-Diamino-3-oxapetane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (52)

Following the same method as in Example 10 except replacing the acid monomer 29 for 25 and replacing 1,5-diamino-3-oxapentane dihydrochloride (Aldrich) for 1,4-xylyldiamine, obtained 52 (52 mg, 55%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1139.

Example 31. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (57)

Following the same method as in Example 10 except replacing the acid monomer 29 for 25 and replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine for 1,4-xylyldiamine, obtained 57 (48 mg, 47%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1183.

Example 32. 1,11-Diamino-3,6,9-trioxaundecane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (63)

Following the same method as in Example 10 except replacing the acid monomer 29 for 25 and replacing 1,11-Diamino-3,6,9-trioxaundecane for 1,4-xylyldiamine, obtained 63 (58 mg, 55%) as a colorless gum. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1227.

Example 33. 1,8-Diamino-3,6-dioxaoctane *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-indolyl))propyl)phenoxyacetamide] (58)

Following the same method as in Example 10 except replacing the acid monomer 30 for 25 and replacing 1,8-diamino-3,6-dioxaoctane (Fluka) for 1,4-xylyldiamine for 1,4-xylyldiamine, obtained 58 (20 mg, 20%) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1259.

Example 34. Ethylenediamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (64)

Following the same method as in Example 10 except replacing the acid monomer 26 for 25 and replacing ethylenediamine dihydrochloride for 1,4-xylyldiamine, obtained

64 (126 mg, 59%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1213.

Example 35. Ethylenediamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (65)

Following the same method as in Example 10 except replacing the acid monomer 29 for 25 and replacing ethylenediamine dihydrochloride for 1,4-xylyldiamine, obtained 65 (79 mg, 42%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+H)^+$ 1073.

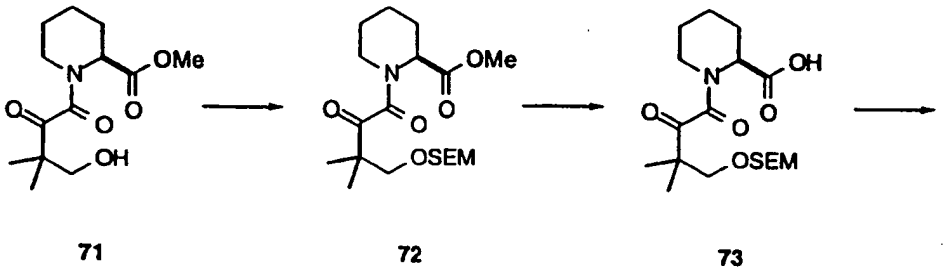
Example 36. *N,N'*-Dimethylethylenediamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3,4-dimethoxyphenyl))propyl)phenoxy-acetamide] (66)

Following the same method as in Example 10 except replacing the acid monomer 26 for 25 and replacing *N,N'*-dimethylethylenediamine for 1,4-xylyldiamine, obtained 66 (118 mg, 55%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+Na)^+$ 1241.

Example 37. *N,N'*-Dimethylethylenediamine *N,N'-bis*[2-(3-((1*R*)-1-((2*S*)-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbonyloxo)-3-(3-pyridyl))propyl)phenoxyacetamide] (67)

Following the same method as in Example 10 except replacing the acid monomer 29 for 25 and replacing *N,N'*-dimethylethylenediamine for 1,4-xylyldiamine, obtained 67 (70 mg, 37%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75MHz) are correct. MS(FAB): $(M+H)^+$ 1101.

Synthetic Overview, part II:



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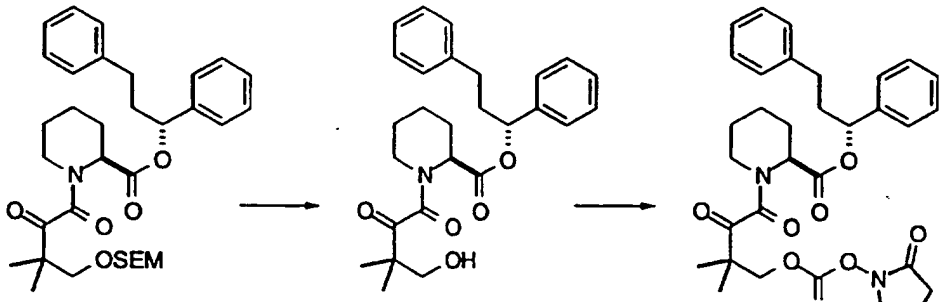

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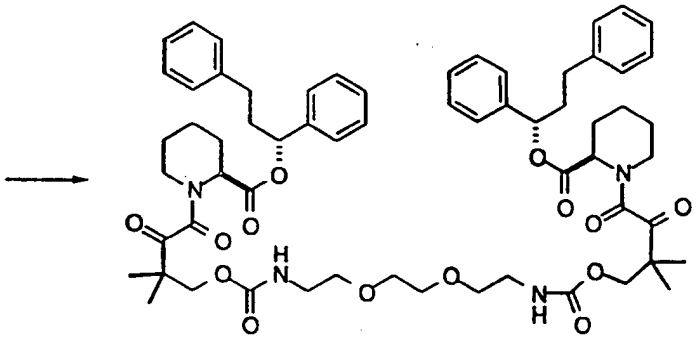

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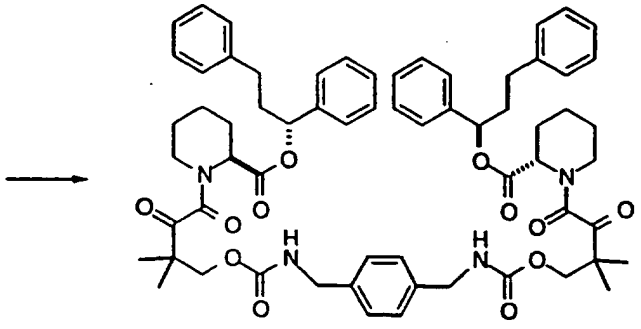

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Synthetic Details

Methyl (2S)-1-(3;3-dimethyl-1,2-diox -4-hydr xy)butyl-2-piperidinecarboxylate, (71)
Prepared according to the procedure reported by D. A. Holt et al., *J. Am, Chem. Soc.* **1993**, *115*, 9925-9938 for the ethyl ester analog.

^{1}H NMR ($CDCl_3$) δ 5.25 (dist d, J=5.2 Hz, 1H), 3.78 (s, 3H), 3.59-3.71 (m, 2H), 3.49 (br d, J=13.8 Hz, 1H), 3.37 (t, J=6.4 Hz, 1H), 3.18 (td, J=12.9, 3.3 Hz, 1H), 2.32 (br d, J=14.0 Hz, 1H), 1.25-1.80 (m, 5H), 1.23 (s, 6H). MS (DCI/NaI) m/z 289 ($M+NH_4$), 272 (M+H).

Methyl (2S)-1-{3,3-dimethyl-1,2-dioxo-4-[2-(trimethylsilyl)ethoxy] methoxy}butyl-2-piperidinecarboxylate, (72)
A solution of methyl (2S)-1-(3,3-dimethyl-1,2-dioxo-4-hydroxy)butyl-2-piperidinecarboxylate, **71** (1.80 g, 6.6 mmol), N,N'-diisopropylethylamine (1.03 g, 8.0 mmol), and 2-(trimethylsilyl)ethoxymethyl chloride (1.33 g, 8.0 mmol) in dichloromethane (25 mL) was stirred at room temperature for 21.5 h. The solution was concentrated and the residue was chromatographed (silica-gel, hexanes-ethyl acetate 10:1 to 6:1 gradient) to give the title compound (2.60 g) as a colorless liquid.

^{1}H NMR ($CDCl_3$) δ 5.22 (br d, J=5.1 Hz, 1H), 4.62 (s, 2H), 3.73 (s, 3H), 3.49-3.71 (m, 5H), 3.14 (td, J=13.3, 3.4 Hz, 1H), 2.28 (br d, J=14.0 Hz, 1H), 1.18-1.77 (m, 5H), 1.30 (s, 3H), 1.27 (s, 3H), 0.84-0.94 (m, 2H), 0.00 (s, 9H). MS (FAB^+/NaI) m/z

(2S)-1-{3,3-Dimethyl-1,2-dioxo-4-[2-(trimethylsilyl)ethoxy]methoxy}butyl-2-piperidinecarboxylic acid, (73)
A mixture of methyl (2S)-1-{3,3-dimethyl-1,2-dioxo-4-[2-(trimethylsilyl) ethoxy]methoxy}butyl-2-piperidinecarboxylate, **72** (2.50 g, 6.2 mmol), 1N lithium hydroxide (9.3 mL) and methanol (10 mL) was stirred at 0°C for 30 min and then at room temperature for 7 h. The mixture was acidified with 1N HCl, diluted with water, and extracted with dichloromethane. The organic extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to give a colorless oil (2.11 g) which was used without further purification.

^{1}H NMR ($CDCl_3$) δ 10.25 (br s, 1H), 5.27 (d, J=4.9 Hz, 1H), 4.61 (s, 2H), 3.68 (dist. t, J=9.4, 9.9 Hz, 1H), 3.49-3.60 (m, 4H), 3.11-3.20 (m, 1H), 2.31 (br d, J=13.7 Hz, 1H), 1.36-1.79 (m, 5H), 1.29 (s, 3H), 1.27 (s, 3H), 0.91 (td, J=8.4, 3.0 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 207.5, 176.9, 168.7, 96.4, 75.0, 66.6, 52.5, 48.8, 45.3, 27.7, 26.2, 23.9 (2 C), 22.6, 19.5, 0.00. MS (FAB^-) m/z 386 (M-H)

(1R)-1,3-Diphenyl-1-pr pyl (2S)-1-{3,3-dimethyl-1,2-dioxo-4-[2-(trimethylsilyl)ethoxy]methoxy}butyl-2-piperidinecarboxylate, (74)

A solution of (2S)-1-{3,3-dimethyl-1,2-dioxo-4-[2-(trimethylsilyl)ethoxy] methoxy}butyl-2-piperidinecarboxylic acid, 73 (1.00 g, 2.6 mmol) and (1R)-1,3-diphenyl-1-propanol (0.72 g, 3.4 mmol) in dichloromethane (10 mL) was treated with N,N-dicyclohexylcarbodiimide (0.70 g, 3.4 mmol) and 4-dimethylaminopyridine (0.22 g, 1.8 mmol). The resulting suspension was stirred at room temperature under a nitrogen atmosphere for 17h. The mixture was then diluted with a small amount of ethyl acetate, filtered, and concentrated, and the residue was subjected to column chromatography (silica-gel, hexanes-ethyl acetate 8:1) to afford the title compound (1.33 g) as a colorless oil

^{1}H NMR ($CDCl_3$) δ 7.14-7.32 (m, 10H), 5.27-5.47 (m, 1H), 5.08 (br d, J=5.2 Hz, 1H), 4.59 (AB q, J_{AB}=6.8 Hz, 2H), 3.66 (dd, J=9.2, 8.6 Hz, 1H), 3.48-3.62 (m, 3H), 3.33 (br d, J=13.1 Hz, 1H), 2.70-2.92 (m, 5H), 2.00 (br d, J=11.5 Hz, 1H), 1.21-1.49 (m, 5H), 1.27 (s, 3H), 1.25 (s, 3H), 0.86-0.95 (m, 2H), 0.00 and -0.02 (2xs, 9H).
MS (FAB^+/NaI) m/z 604 (M+Na). Exact Mass: Calc. (M+Na) for $C_{33}H_{47}NSiO_6$, 604.3070 ; found, 604.3073.

(1R)-1,3-Diphenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxo-4-hydroxy)butyl-2-piperidinecarboxylate, (75)

A solution of (1R)-1,3-diphenyl-1-propyl (2S)-1-{3,3-dimethyl-1,2-dioxo-4-[2-(trimethylsilyl)ethoxy]methoxy}butyl-2-piperidinecarboxylate, **74** (0.75 g, 1.3 mmol) and 48 wt% HF (0.5 mL) in acetonitrile (25 mL) was stirred at room temperature for 4 h, and then partitioned between 10% aqueous sodium bicarbonate and ethyl acetate. The organic layer was decanted, washed with water, dried over anhydrous sodium sulfate, and concentrated, and the residue chromatographed (silica-gel, hexanes-ethyl acetate 4:1 to 2:1 gradient) to afford **75** (0.45 g) as a colorless oil).

^{1}H NMR ($CDCl_3$) δ 7.10-7.27 (m, 10H), 5.38-5.47 (m, 1H), 5.04 (br d, J=5.3 Hz, 1H), 3.47-3.621 (m, 3H), 3.29 (br d, J=13.9 Hz, 1H), 2.67-2.93 (m, 5H), 2.00 (br d, J=12.8 Hz, 1H), 1.17-1.57 (m, 5H), 1.15 (s, 3H), 1.14 (s, 3H). MS (FAB^+/NaI) m/z 474 (M+Na). Exact Mass: Calc. (M+Na) for $C_{25}H_{33}NO_5$, 474.2256; found, 474.2273.

(1R)-1,3-Diphenyl-1-propyl (2S)-1-[3,3-dimethyl-1,2-dioxo-4-(1-succinimidyl xycarbonyl) xy]butyl-2-piperidinecarboxylate, (76)

A solution of (1R)-1,3-diphenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxo-4-hydroxy)butyl-2-piperidinecarboxylate, 75 (223 mg, 0.49 mmol) in dichloromethane (13 mL) was treated with N,N-diisopropylethylamine (0.8 mL), and N,N'-disuccinimidyl

carbonate (385 mg), and the mixture stirred at room temperature for 66 h. It was then washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated to afford a yellow oil (280 mg) which was used without further purification.

^{1}H NMR (C_6D_6) δ 7.11-7.32 (m, 10H), 5.56-5.65 (m, 1H), 5.36 (br d, J=5.1 Hz, 1H), 4.51 (d, J=10.5 Hz, 1H), 4.17 (d, J=10.5 Hz, 1H), 3.52 (br d, J=13.4 Hz, 1H), 2.71-3.11 (m, 5H), 1.99 (br d, J=14.4 Hz, 1H), 1.70 (br s, 4H), 1.01-1.38 (m, 11H). ^{13}C NMR (C_6D_6) δ 205.4, 171.0, 169.7, 168.2, 153.5, 139.2 (139.0), 131.2, 130.2, 130.1, 129.8, 129.5, 129.2, 128.3 (128.2), 77.9, 76.9, 53.1, 48.4, 45.3, 41.9, 41.8, 27.7, 26.6 (2C), 26.3, 23.5, 22.5, 22.3. MS (FAB$^+$/NaI) m/z 615 (M+Na), 474, 434. Exact Mass: Calc. (M+Na) for $C_{32}H_{36}N_2O_9$, 615.2319; found, 615.2299.

2,2-(Ethylenedioxy)diethylamine N,N'-{2,2-dimethyl-3,4-dioxo-4-{(2S)-2-[(1R)-1,3-diphenylpropyloxycarbonyl]-1-piperidinyl}butylcarbamate, (77)

A solution of (1R)-1,3-diphenyl-1-propyl-(2S)-1-[3,3-dimethyl-1,2-dioxo-4-(1-succinimidyloxycarbonyl)oxy]butyl-2-piperidinecarboxylate, **76** (75 mg, 0.13 mmol) and N,N-diisopropylethylamine (66.3 μL) in acetonitrile (4 mL) was treated with 2,2'-(ethylenedioxy)diethylamine (9.3 μL), and the mixture stirred at room temperature for 21 h. The solvent was removed and the residue chromatographed (silica-gel, hexanes-ethyl acetate 1:3 to 1:2 gradient) to give the title compound (20 mg) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 7.10-7.55 (m, 20H), 5.48 (br dd, J=12.2, 6.1 Hz, 2H), 5.20-5.35 (br s, 2H), 5.09-5.18 (m, 2H), 4.22 (AB q, J_{AB}=10.6 Hz, 4H), 3.48-3.80 (m, 8H), 3.20-3.45 (m, 6H), 2.80-3.15 (m, 10H), 1.98-2.08 (m, 2H), 1.17-1.68 (m, 22H). ^{13}C NMR ($CDCl_3$) δ 205.3, 170.1, 166.9, 156.6, 137.6, 137.3, 129.7 (2C), 128.9, 128.8, 127.1, 127.0, 76.9, 70.6, 70.4, (69.9), (60.8), (56.9), 51.6, 47.3, (47.2), 44.0, 41.2, 40.7, 40.5, (40.2), (39.0), (28.1), 26.8, 25.2, (24.7), 22.3, (22.2), 21.8, (21.4), 21.0, (20.8), 14.6. MS (FAB$^+$/NaI) m/z 1125 (M+Na).

***p*-Xylylenediamine N,N'-{2,2-dimethyl-3,4-dioxo-4-{(2S)-2-[(1R)-1,3-diphenylpropyloxycarbonyl]-1-piperidinyl}butylcarbamate, (78)**

A solution of *p*-xylylenediamine in dimethylformamide (0.1 mM, 0.5 mL) was added dropwise, over a 30 min-period, to a solution of **76** (66 mg, 0.11 mmol) and triethylamine (46 μL) in acetonitrile (1 mL). The mixture was then partitioned between ethyl acetate and water, and the organic layer was decanted, washed with water, dried over anhydrous sodium sulfate, and concentrated to a yellow oil. Column chromatography (silica-gel, hexanes-ethyl acetate 1:1) afforded the title compound (33 mg) as a colorless oil.

^{1}H NMR (C_6D_6) δ 7.34-7.55 (m, 24H), 5.72-5.85 (m, 2H), 5.64-5.68 (m, 2H), 5.35-5.45 (m, 2H), 4.77 (AB q, J_{AB}=10.8 Hz, 4H), 4.46-4.57 (m, 4H), 3.64 (br d, J=12.2 Hz, 2H), 2.92-3.25 (m, 10H), 2.14 (br d, J=13.2 Hz, 2H), 1.20-1.75 (m, 22H).
MS (FAB^+/NaI) m/z 1113 (M+Na).

Cell-based transfection assay

In general, dimerizer assays were carried out as follows. Human 293 cells were transiently transfected by calcium phosphate procedure with plasmids PCGNNGF3 and PCGNNF3VP16, expressing Gal4 DNA binding domain (aa 1-147) fused to 3 copies of FKBP12 and 3 copies of FKBP12 fused to the VP16 activation domain (aa 411-490), respectively. The reporter plasmid (G5IL2-SEAP) used in these assays contains a gene that encodes for secreted alkaline phosphatase (SEAP) under the control of the minimal IL2 promoter and 5XGAL4 binding sites placed upstream of the promoter. In all cases, a plasmid expressing growth hormone was used as an internal control to moniter transfection efficiency.

Approximately, 16 hrs after transfection, the media was removed and the cells were washed twice with PBS. Cells were refed with 2.5 ml of DMEM containing 10% serum and two hours later, synthetic dimerizers were added directly to the medium at appropriate concentrations in 5ul of ethanol carrier solution. Approximetely, 24 hrs after the addition of the drugs, 100 ul of the media was removed and assayed for SEAP activity and another 100 ul of the media was used to assay for growth hormone activity (to normalize for transfection efficiency).

Results for a sample of our multimerizers in that system are shown below at multimerizer concentrations from 0.1 to 10^4 nM, as indicated, normalized for hGH expression, and expressed as a % of maximal transcriptional activity observed with the prototype multimerizer, FK1012 (see Spencer et al, Science, supra). It should be appreciated that multimerizers of this invention will vary somewhat in their observed activity, depending on the particular chimeric proteins and other components of such systems. We recommend that the practitioner select multimerizers based on their performance in the particular system of interest.

Dimerizer Assay Worksheet

Activation Domain: VP16 *Ratio VP16/Gal4:* 10:01
DNA Binding Domain: Gal4 *Reporter Gene:* G5IL2-SEAP

Cmpd	% of FK1012 Max. Activity				
	1	10	100	1,000	10,000
FK1012	17.38	17.24	100.00	70.87	
53		3.49	6.17	12.62	55.12
35		7.87	2.91	2.76	2.62

Cmpd	% of FK1012 Max. Activity				
	1	10	100	1,000	10,000
FK1012		36.67	100.00	54.19	
53		4.79	6.42	31.09	57.67
37		4.05	2.98	5.88	10.49
48		5.72	6.56	24.79	47.56
59		5.56	5.28	40.72	36.02

Cmpd	% of FK1012 Max. Activity				
	0.1	1	10	100	1,000
FK1012	24.28	25.67	30.74	100.00	
60	24.24	27.84	49.66	21.28	
54	26.84	30.61	57.48	29.67	
49	19.74	19.26	54.90	76.59	
50	20.25	20.19	26.24	58.99	
52	23.40	25.12	31.51	56.54	
47	23.26	25.15	42.75	25.14	

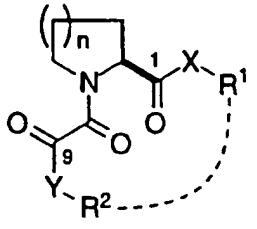
What is claimed is:

1. A multimerizing agent of the formula

$$M^1\text{-}L\text{-}M^2$$

I

where M^1 and M^2 are independently moieties of the formula:



II

where n = 1 or 2;

X = O, NH or CH_2;

Y = O, NH, NR^3, or represents a covalent bond from R^2 to atom 9;

R^1, R^2, and R^3 are independently C_1-C_{20} alkyl or aryl;

wherein alkyl includes both saturated and unsaturated, straight chain, branched, cyclic, or polycyclic aliphatic hydrocarbons which may contain oxygen, sulfur, or nitrogen in place of one or more carbon atoms, and which are optionally substituted with one or more functional groups selected from the group consisting of hydroxy, C_1-C_8 alkoxy, acyloxy, carbamoyl, amino, N-acylamino, ketone, halogen, cyano, carboxyl, and aryl;

aryl includes stable cyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated C_3-C_{14} moieties; which may further be substituted with one to five members selected from the group consisting of hydroxy, C_1-C_8 alkoxy, C_1-C_8 branched or straight-chain alkyl, acyloxy, carbamoyl, amino, N-acylamino, nitro, halogen, trifluoromethyl, cyano, and carboxyl;

R^1 and R^2 may optionally be covalently linked together, forming a macrocyclic structure (as indicated by the dashed line in II); and

L is a linker moiety joining monomers M^1 and M^2 through covalent bonds to either R^1 or R^2, not necessarily the same in each of M^1 and M^2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :540/455, 460, 461; 546/189, 208; 548/524, 523, 518
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/455, 460, 461; 546/189, 208; 548/524, 523, 518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,120,727 (KAO ET AL) 09 June 1992, see abstract.	1
X	US, A, 5,162,333 (FAILLI ET AL) 10 November 1992, see abstract.	1
A	SCIENCE, Volume 262, issued 21 November 1993, Spencer et al, "Controlling Signal Transduction with Synthetic Ligands", pages 1019-1024, see page 1019, Figure 1.	1
X	PEPTIDE CHEMISTRY 1993, Volume 31, Number 1, issued 1994, Uchiyama et al, "Synthesis of Hybrid Type of Anti-HIV Drugs", pages 89-92, see compound 25, page 92.	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
13 NOVEMBER 1995

Date of mailing of the international search report
13 DEC 1995

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10559

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	WO, A, 94/18317 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY ET AL) 18 August 1994, see example 14, page 69, example 16, page 70, and example 18, page 71.	1
X, P	WO, A, 95/02684 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY ET AL) 26 January 1995, see example 14, page 73 and examples 16 and 18, page 74.	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10559

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10559

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 471/04, 471/10, 471/14, 471/20, 471/22, 487/04, 487/10, 487/14, 487/20, 487/22, 491/04, 491/044, 491/10, 491/107, 491/14, 491/147, 491/153, 491/20, 491/22, 495/04, 495/10, 495/14, 495/20, 495/22, 497/04, 497/10, 497/14, 497/20, 497/22

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim 1, drawn to compounds, wherein R1 and R2 do not covalently join to form a macrocyclic moiety in either M1 or M2.

Group II, claim 1, drawn to compounds, wherein R1 and R2 covalently join to form a macrocyclic moiety in both M1 and M2.

Group III, claim 1, drawn to compounds, wherein R1 and R2 covalently join to form a macrocyclic moiety in M1, but not in M2.

The inventions listed as Groups I, II, and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: no significant structural element is shared by all of the Markush alternatives among the three Groups because the compounds in these Groups share only L in their structures, but L is only a small portion of their structures and L does not constitute a structurally distinctive portion of the molecules. Additionally, all the compounds in the Markush claim do not belong to an art recognized class ofchemical compounds. The special technical feature of the invention of Group I is compounds with no macrocyclic moiety. However, the special technical feature of the invention of Group II is compounds with two macrocyclic moieties, while the special technical feature of the invention of Group III is compounds with only one macrocyclic moiety. The special technical features of the three Groups differ.